

The Effects of Nonpharmacologic Interventions on Cognitive Function in Patients With Cancer: A Meta-Analysis

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Problem Identification: To evaluate the effects of nonpharmacologic interventions on cognitive functioning in adult patients with cancer.

Literature Search: EMBASE, MEDLINE®, Cochrane Library CENTRAL, CINAHL®, and Korean databases.

Data Evaluation: Cochrane's risk of bias for randomized studies and the RevMan, version 5.3, program of the Cochrane Library were used.

Synthesis: Fourteen controlled trials with a total of 977 participants met the inclusion criteria. Overall, nonpharmacologic interventions had beneficial effects on subjective cognitive functioning and memory, but not on attention, executive functioning, and verbal ability. In the subgroup analyses by approach type, psychological interventions had a significant effect on perceived cognitive function.

Conclusions: The findings suggest that nonpharmacologic interventions, particularly psychological interventions, may have a positive impact on perceived cognitive functioning and memory in patients with cancer. Additional research with adequate power is required to determine the effectiveness of behavioral intervention as a cognitive rehabilitation strategy.

Implications for Practice: Cognitive function would be most improved in patients with cancer when a multimodal intervention approach (education, retraining, and physical activity) is employed.

Cognitive impairment is one of the most frequently reported adverse effects of chemotherapy (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012). Data suggest that 15%–45% of patients who undergo chemotherapy experience loss of memory and attention problems, are unable to concentrate or multitask, or lose cognitive control, which negatively affects their quality of life (Hermelink et al., 2008; Matsuda et al., 2005; Schagen et al., 1999; Vardy & Tannock, 2007; Wefel & Schagen, 2012). Neuroimaging studies have shown reduced gray and white matter volume in multiple brain sites following chemotherapy, including the prefrontal, hippocampal, and parahippocampal areas (de Ruiter et al., 2011).

An increase in the awareness of chemotherapy-related cognitive impairments is reflected by the growth in the number of review articles focused on the structural and functional concomitants of chemotherapy in the human brain (Kaiser, Bledowski, & Dietrich, 2014). Five meta-analyses have suggested that cancer treatments are associated with cognitive deficits in patients compared with population norms and controls. These deficits are primarily in executive functioning, verbal ability, and visuospatial ability, albeit with a relatively small to medium effect size in each of these domains (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Jim et al., 2012; Prabhu et al., 2014; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006).

Two approaches to treat chemotherapy-related cognitive impairments have been evaluated in clinical trials: pharmacologic interventions and (neuro) psychological interventions, the latter of which refers to cognitive training programs aimed at either treating the cognitive deficits or providing education on how to manage them (Gehring, Roukema, & Sitskoorn, 2012). Cognitive training can be divided into the two most frequently used approaches, strategy training and retraining. Strategy training teaches patients to apply coping strategies to their cognitive impairment, which helps patients to focus on their rehabilitation by adjusting the certain environment (minimizing the distraction) and, therefore, be able to anticipate getting better. Retraining instructs patients to repetitively practice the same exercises (e.g., stimulation) to restore attention, memory, and executive functioning. Increasingly, retraining is being administered by computer-based programs (Gehring et al., 2012).

Although a growing body of literature exists on interventions to manage cognitive deficits, only two systematic reviews have investigated interventions for managing cognitive deficits in patients with cancer (Gehring et al., 2012; Gehring, Sitskoorn, Aaronson, & Taphoorn, 2008). These reviews reveal that cognitive training may improve self-reported cognitive symptoms. Cognitive training may be a more attractive option than pharmacologic treatments because it is less invasive. Several studies have found that nonpharmacologic interventions improve attention (Cimprich, 1993; Cimprich & Ronis, 2003; Gehring et al., 2009; Goedendorp, Knoop, Gielissen, Verhagen, & Bleijenberg, 2014; Oh et al., 2010; Von Ah et al., 2012) and increase well-being in patients with cancer (Locke et al., 2008; Milbury et al., 2013; Oh et al., 2010). However, other studies have not found an effect of nonpharmacologic interventions on cognitive function (Cherrier et al., 2013; Goedendorp et al., 2014; Kesler et al., 2013; Milbury et al., 2013; Poppelreuter, Weis, & Bartsch, 2009).

Meta-analysis is a recognized method for synthesizing results of controlled trials to estimate the overall effect size of an intervention and an ideal technique to help reconcile these conflicting data (Sheinfeld Gorin et al., 2012). Therefore, the goal of this study was to conduct a meta-analysis that examines cognitive function changes after nonpharmacologic interventions to determine whether the intervention can affect cognitive functioning in patients with cancer.

Although several previous meta-analyses have examined cognitive functioning in patients treated with chemotherapy, no meta-analysis has been conducted to determine the effectiveness of nonpharmacologic interventions on cognitive function in cancer survivors. Therefore, this review was conducted to identify

the best available evidence regarding the effects of nonpharmacologic interventions on cognitive functioning in patients with cancer. Because intervention characteristics such as intervention type were the moderators of intervention efficacy (Faller et al., 2013), the authors have examined the treatment effect by performing subgroup analysis.

Methods

This meta-analysis is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati et al., 2009). The eligibility criteria are detailed in accordance with the PICOS (Participant, Intervention, Control, Outcome, Study design) framework.

Participants were adults aged 18 years or older who were diagnosed with cancer of any type and any tumor stage. Nonpharmacologic (psychological or behavioral) interventions for the management of cognitive deficits were considered. The authors defined nonpharmacologic interventions as any non-drug intervention administered with the intention of preventing or ameliorating cognitive deficits following chemotherapy. Psychological interventions included (but were not limited to) retraining, education, and compensation strategies. Behavioral interventions designed to prevent or ameliorate chemotherapy-related cognitive deficits also were included. Behavioral interventions included physical exercise and activities, such as walking or gentle movements. Studies that concomitantly administered pharmacologic and nonpharmacologic interventions were excluded. No treatment (e.g., standard care) and attention or placebo control conditions were considered.

The primary outcome was cognitive performance as assessed by neuropsychological tests and self-reported via questionnaires. The authors included general functioning—including mood/psychiatric symptoms, self-reported fatigue, and quality-of-life measurements—as the secondary outcomes. Both randomized, controlled trials (RCTs) and non-RCTs were considered. The authors included studies in which cognitive functioning was measured at baseline and following an intervention at any time point.

Search Strategy

To identify the relevant studies, the authors performed an electronic database search through EMBASE, MEDLINE®, Cochrane Library CENTRAL, CINAHL®, and Korean databases. In addition, the authors searched the Google Scholar® database and reference lists of screened studies. The main keywords used in the search indicated *cognitive training intervention*, *people with cancer*, and *study design*,

combined. Searches were inclusive of studies in Korean or English from the earliest publication date available through November 2014.

Study Selection

All studies identified through the electronic searches were downloaded to RefWorks, a reference management database, and duplicates were removed. Two authors independently screened citations of studies, then assessed the full text of eligible citations for inclusion.

Studies were included if they (a) focused on adult patients with cancer (aged 18 years or older), (b) measured cognitive training interventions, (c) measured cognitive function, (d) were controlled trials (RCTs or non-RCTs), and (e) included sufficient data for the calculation of effect sizes between the treatment and control groups for the meta-analysis.

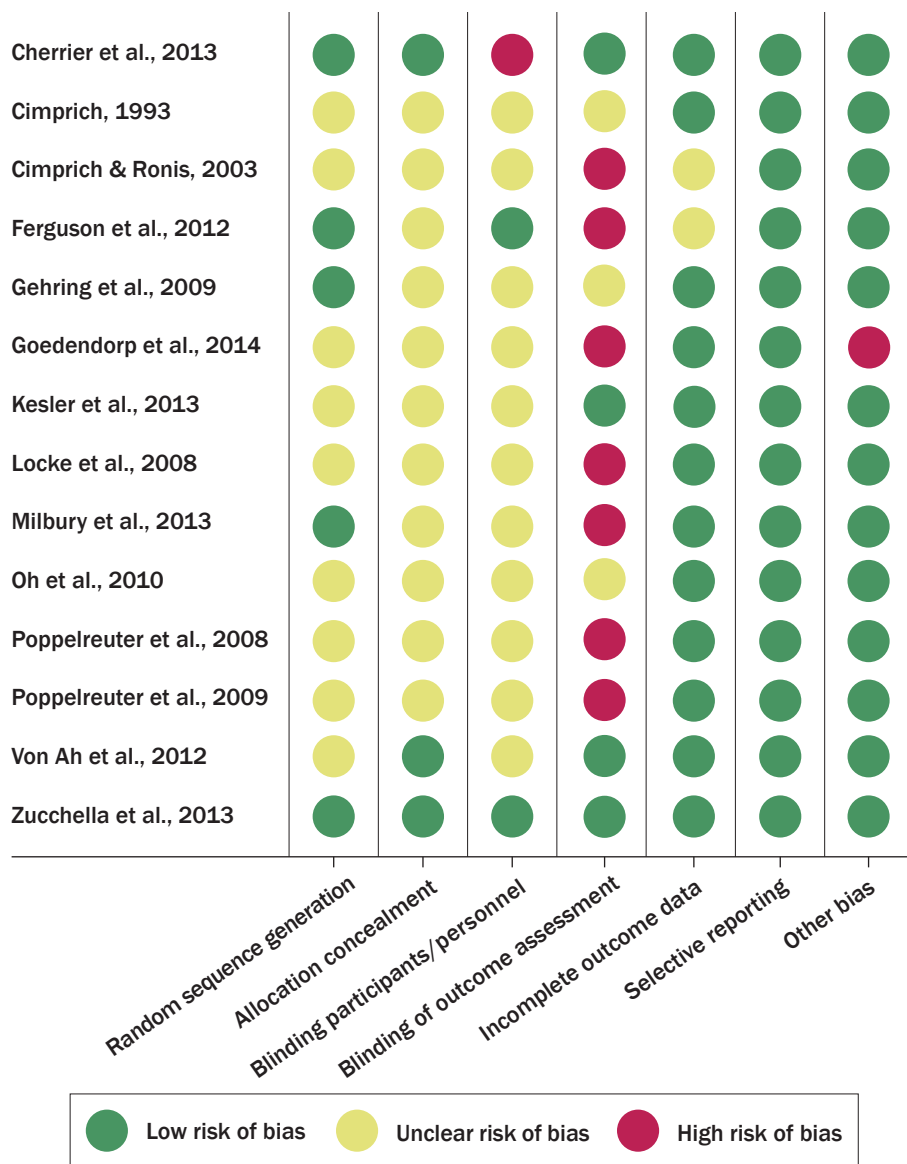
Data Extraction

The following information was extracted from each study based on a predesigned data extraction form: (a) article details (authors, year, country), (b) study design, (c) sample information (age, stage, cancer type), (d) description of the intervention (type, mode of delivery, provider, duration), (e) control conditions, (f) outcomes and instruments, and (g) results of cognitive functioning.

For continuous outcomes, the authors extracted the final value, the standard deviation, and the number of patients assessed at each endpoint for each treatment arm to estimate the mean difference and standard error between the treatment arms.

Risk of Bias Assessment

Studies were assessed for methodologic quality using a seven-item Risk of Bias scale, which was developed by the Cochrane Bias Method Group (Higgins & Green, 2011). In addition, the authors also assessed the monitoring procedures and the use of manuals of the intervention. These are considered to be crucial



Note. Sequence generation and allocation concealment were at risk for selection bias, blinding of participants and personnel was at risk for performance bias, blinding of outcome was at risk for detection bias, incomplete data was at risk for attrition bias, and selective reporting was at risk for reporting bias.

FIGURE 1. Risk of Bias Summary for Included Studies

for the risk of bias assessment in nonpharmacologic intervention studies (Ranchor et al., 2012).

Pilot testing was performed on three studies by two independent reviewers before the independent assessment of study quality for all studies. Disagreements were resolved during meetings between the authors. Studies were assessed in relation to the five sources of bias. These include selection bias, performance bias, attrition bias, detection bias, and reporting bias (see Figure 1). The authors interpreted and reported all bias criteria as having a low, high, or unclear risk of bias. The authors reported an unclear risk of bias when insufficient information was

provided or when uncertainty over the potential for bias was present.

Measures of Treatment Effect

Meta-analyses were performed in RevMan, version 5.3. When calculating the mean effect size, each was weighted by its inverse variance, giving more weight to the studies with larger sample sizes (Higgins & Green, 2011). Random effect models were applied to calculate the effect sizes, which account for variance difference between the studies and participants within studies (Smedslund & Ringdal, 2004). Standardized mean difference greater than zero indicated a significant effect favoring the intervention. Heterogeneity was examined using the I^2 statistic, which measured the percentages of total variation across studies determinable to heterogeneity rather than chance. An I^2 of 25% indicated low heterogeneity, I^2 of 50% was considered moderate, and I^2 of 75% was considered high (Higgins & Green, 2011).

The authors used a funnel plot to assess the degree of publication bias. Effect sizes were plotted according to respective standard error, and the symmetry of these plots were evaluated. The authors considered publication bias to exist if there were no small studies without statistically significant effects (Higgins & Green, 2011). Egger's test was then performed to examine for publication bias (Egger, Smith, Schneider, & Minder, 1997).

Results

After eliminating duplications, 4,360 studies were screened. The authors identified 38 potentially relevant studies from the screening of titles and abstracts and a full review was conducted on those 38 studies. Of the studies, 27 failed to meet the eligibility criteria: 9 studies did not provide sufficient data for the computation of the effect size, 8 studies had nonrelevant interventions, 6 studies were descriptive, and 4 studies had non-relevant outcomes. Three studies were retrieved by a manual search of the reference lists. A total of 14 English-language studies were selected for final inclusion: 11 studies were used for meta-analysis and 3 studies were included only for systematic review because of the insufficient statistical data.

Table 1 describes the characteristics of the 14 studies. More than half of the studies were conducted in the United States. All studies used an RCT design. The cancer types studied were breast ($n = 7$), brain ($n = 3$), hematologic ($n = 1$), and mixed types ($n = 3$). Of the 14 studies included in the analyses, three reports were studies of patients with brain tumors in which only some of the patients received chemotherapy. One study did not include a descrip-

tion of chemotherapy treatment or nontreatment. The remaining 10 studies described participants ($n = 614$) who received chemotherapy. Seven trials included patients with stage I–III cancer. Three trials included patients across all stages of cancer. The cancer stage of the patients in the remaining four trials was unclear. The mean age of the study participants was 53.1 years. The sample size across the 14 studies varied from 13–157 patients, and the total was 977 participants. An individual-based cognitive rehabilitation approach ($n = 10$) was the most frequent treatment format, and interventions were provided both in the patient's home and at the clinic. The number of sessions varied from 4–36 ($\bar{X} = 16.2$ sessions). The time per session varied from 25–120 minutes ($\bar{X} = 60.71$ minutes). Nonpharmacologic interventions were divided into two approaches: psychological ($n = 11$) and behavioral ($n = 3$). Three studies used computer-based retraining programs to restore attention, memory, or executive functioning. Most cognitive rehabilitation programs were administered by a neuropsychologist ($n = 6$). Interventions were delivered by experienced occupational therapists in five studies and nurses in two studies. Among the 14 studies, the duration of the intervention ranged from two weeks to more than one year. All studies used standard care control groups.

Outcome Measures

The primary outcome was cognitive functioning, which was evaluated as perceived cognitive functioning ($n = 5$), attention ($n = 6$), memory ($n = 8$), executive function ($n = 7$), verbal ability ($n = 3$), and multiple areas of cognitive function ($n = 7$). The most commonly used measures of perceived cognitive function were the Functional Assessment of Cancer Therapy–Cognitive and European Organisation for Research and Treatment of Cancer assessment tools. The objective measures of cognitive functioning are listed in Table 2, and the most commonly used tools to evaluate attention were the digit span (DS) test and Trail Making Test (TMT). Measures, such as the Rey Auditory Verbal Learning Test (RAVLT), Visual Verbal Learning Test (VVLTL), and digit symbol test were used to test general memory. Category fluency was commonly used to evaluate executive functioning. For multiple areas of cognitive functioning, the Wechsler Adult Intelligence Scale–III (WAIS-III) and the Repeatable Battery of the Assessment of Neuropsychological Status (R-BANS) were used as the standardized assessment tools.

Study Quality

Of the 14 studies, only 5 reported adequate details on the randomization sequence. Nine studies with an

TABLE 1. Descriptive Summary of Included Studies

Study	Design	Intervention Group	Control Group	Outcomes
Cherrier et al., 2013 USA	RCT of patients with various cancer types with experimental (n = 12) and control (n = 16) groups; all received chemotherapy.	Cognitive rehabilitation intervention in a group setting; providers were unclear; seven sessions for seven weeks, 60 minutes per session; mean age was 60.5 years.	No intervention; mean age was 57.8 years.	Quality of life, mood and symptom measures, and neurocognitive tests
Cimprich, 1993 USA	RCT of patients with breast cancer at stages I–II with experimental (n = 16) and control (n = 16) groups; some received chemotherapy (59%).	Attention-restoring activities in an individual (home) setting; nurse providers; three sessions per week for 90 days, 20–30 minutes per session; mean age was 57 years.	Wait list; mean age was 51 years.	Total attentional score
Cimprich & Ronis, 2003 USA	RCT of patients with breast cancer at early stage with experimental (n = 83) and control (n = 74) groups; no description of chemotherapy.	Home-based program (based in a natural environment); oncology nurse providers; session totals unclear, but about 30 minutes in length per session; mean age was 51.9 years.	Standard care; mean age was 55.9 years.	Total attentional score
Ferguson et al., 2012 USA	RCT of patients with breast cancer at stages I–II with experimental (n = 19) and control (n = 21) groups; all received chemotherapy.	Memory and attention adaptation training in an individual format at a medical center; clinical psychologist provider; sessions took place during eight weeks, 30–50 minutes per session; mean age was 51.2 years.	Wait list; mean age was 49.4 years.	Cognitive function, quality of life, and neuropsychological outcomes
Gehring et al., 2009 Netherlands	RCT of patients with glioma at stages II–III with experimental (n = 70) and control (n = 70) groups; some received chemotherapy (11%).	Cognitive rehabilitation program (computer-based and psychoeducation) in an individual format at home or in the hospital; neuropsychologist provider; six sessions for six weeks, 120 minutes per session; mean age was 42 years.	Usual care (wait list); mean age was 43.8 years.	Neuropsychological tests for attention, verbal memory, and executive function; cognitive symptoms
Goedendorp et al., 2014 Netherlands	RCT of patients with various cancer types with experimental (n = 50) and control (n = 48) groups; some received chemotherapy (72%).	Cognitive behavioral therapy in an individual format; three therapists with cognitive behavioral therapy were providers; 5–26 sessions plus two booster sessions in a six-month period, 60 minutes per session; mean age was 44.6 years.	Wait list; mean age was 45.3 years.	Self-reported cognitive impairments and neuropsychological tests
Kesler et al., 2013 USA	RCT of patients with breast cancer at stages I–III with experimental (n = 21) and control (n = 20) groups; some received chemotherapy (63%).	Executive function training program (computerized program) in an individual format for the home setting; neuropsychologist provider; 48 sessions for 12 weeks, 20–30 minutes each; mean age was 55 years.	Wait list; mean age was 56 years.	Cognitive flexibility, verbal memory, working memory, processing speed, distress, and cognitive fatigue
Locke et al., 2008 USA	RCT of patients with primary brain tumor at mixed grade with experimental (n = 8) and control (n = 5) groups; some received chemotherapy (69%).	A cognitive rehabilitation intervention and a problem-solving therapy intervention in a group setting at a medical center; psychologist/neuropsychologist providers; 12 sessions for four weeks, 100 minutes each; mean age was 46.5 years.	Standard care; mean age was 60 years.	Quality of life, functional capacity, cognitive function, mood, and fatigue

(Continued on the next page)

^a Not included in the meta-analysis
 RCT—randomized, controlled trial

TABLE 1. Descriptive Summary of Included Studies (Continued)

Study	Design	Intervention Group	Control Group	Outcomes
Milbury et al., 2013 USA	RCT of patients with breast cancer at stages I–III with experimental (n = 23) and control (n = 24) groups; all received chemotherapy.	Tibetan sound meditation program in an individual format; providers were three meditation instructors; 12 sessions for six weeks, 60 minutes each; mean age was 53 years.	Wait list; mean age was 54.1 years.	Cognitive function, quality of life, depressive symptoms, sleep disturbance, fatigue, spirituality, and digit span/verbal memory/executive function
Oh et al., 2010 Australia	RCT of patients with various cancer types with experimental (n = 23) and control (n = 31) groups; All received chemotherapy.	Qigong program in a group setting in a hospital; provider was an experienced Qigong instructor; 10 sessions for about 10 weeks, 90 minutes each; mean age was 64.6 years.	Usual health care; mean age was 61.1 years.	Self-reported cognitive function, quality of life, inflammation
Poppelreuter et al., 2008 ^a Germany	RCT of patients with hematologic cancer with experimental 1 (n = 33), experimental 2 (n = 34), and control (n = 29) groups; some received chemotherapy (75%).	Group 1 had neuropsychological training and group 2 had computer-based training, all provided in an individual format in a hospital setting; providers were occupational therapists; 12–20 sessions for 3–5 weeks, 60 minutes each; mean age was 42.6 years.	No treatment; mean age was unclear.	Cognitive functioning, mental fatigue, and distractibility and retardation in mental tasks
Poppelreuter et al., 2009 Germany	RCT of patients with breast cancer at stages I–II with experimental 1 (n = 33), experimental 2 (n = 34), and control (n = 29) groups; all received chemotherapy.	Group 1 had neuropsychological training; group 2 had computer-based training; all provided in an individual format in a hospital setting; providers were specialized occupational therapists; four sessions for four weeks, 60 minutes each; mean age was 49.2 years.	No treatment; mean age was unclear.	Cognitive functioning, mental fatigue, and distractibility and retardation in mental tasks
Von Ah et al., 2012 ^a USA	RCT (post only) of patients with nonmetastatic breast cancer with experimental 1 (n = 26), experimental 2 (n = 27), and control (n = 29) groups; all received chemotherapy.	ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly trial); 3–5 person group in a clinical setting; providers were trained interventionists; 10 sessions for 6–8 weeks, 60 minutes each; mean age was 55.2 years in group 1 and 56.9 years in group 2.	Wait list; mean age was 57.2 years.	Immediate memory composite, delayed memory composite, speed of processing composite, perceived cognitive functioning, symptom distress, quality of life, and satisfaction/acceptability
Zucchella et al., 2013 ^a Italy	RCT (post only) of patients with primary brain tumors at mixed grade with experimental (n = 25) and control (n = 28) groups; no chemotherapy.	Cognitive rehabilitation (computer-based) in an individual format; two psychologist providers; 16 sessions for four weeks, 60 minutes each; mean age was 58.7 years.	Usual care; mean age was 52.7 years.	Cognitive function; verbal and spatial immediate memory; verbal, immediate, and delayed memory; nonverbal reasoning; frontal functionality; simple speed processing and complex attention; visual selective attention; verbal fluency; and visuo-constructional abilities

^a Not included in the meta-analysis
RCT—randomized, controlled trial

unclear risk of bias reported the use of a randomization method, but the method could not be identified. Three of the 14 studies had a low risk of bias, but did not provide details about the allocation concealment. For 11 studies, it was unclear whether both the patients and intervention providers were blind to the intervention. Only two studies stated that the intervention provider or participant was blind to the group allocation (Ferguson et al., 2012; Zucchella et al., 2013), and one study was rated as high risk because the intervention providers were not blind to the intervention (Cherrier et al., 2013). Four studies (29%) reported that the individual conducting the outcome assessment was blind to condition (Cherrier et al., 2013; Kesler et al., 2013; Von Ah et al., 2012; Zucchella et al., 2013). Of the remaining 10 studies, seven were rated as high risk for bias and three were rated with an unclear risk of bias (Cimprich, 1993; Gehring et al., 2009; Oh et al., 2010). Twelve studies included reasons for participant dropout, which were unlikely to be related to outcomes. Therefore, the current authors evaluated participant dropout as low risk for attrition bias. For all studies, the prespecified expected outcome of interest was reported, and, therefore, all were judged to be low risk for reporting bias. The monitoring procedures and the use of manuals of the intervention are considered to be crucial for the risk of bias assessment in nonpharmacologic intervention studies (Ranchor et al., 2012). Thirteen studies provided an intervention manual and evaluated the intervention procedure. Therefore, the authors judged those 13 studies as low risk for other sources of bias; the remaining study was judged as high risk.

Meta- and Subgroup Analysis

The results of the analysis revealed effect sizes with 95% confidence. Statistical heterogeneity was observed between study estimates ($I^2 = 0\%–68\%$). The current meta-analysis revealed significant treatment effects on memory and perceived cognitive functioning. The weighted average effect size for memory ($n = 8$) was 0.21 (95% confidence interval [CI] [0.04, 0.38], $p = 0.02$, $I^2 = 0\%$), indicating a small effect size. A significant small effect on perceived cognitive functioning ($n = 5$) also was observed ($d = 0.41$, 95% CI [0.2, 0.61], $p < 0.001$, $I^2 = 0\%$). No effects were noted on cognitive performance as measured by tests of attention, executive functioning, and verbal ability. The effect sizes of the funnel plot revealed a symmetry of outcomes. In addition, when Egger's test was performed, the funnel plot asymmetry was not significant ($p = 0.858$). No significant effects were noted on quality of life ($p = 0.58$), fatigue ($p = 0.24$), depression ($p = 0.61$), or anxiety ($p = 0.6$). Some heterogeneity was observed between these study estimates ($I^2 = 37\%–87\%$).

For subgroup analysis, the nonpharmacologic interventions were divided into two categories, psychological and behavioral. In this analysis, a significant effect of the psychological intervention on perceived cognitive function ($n = 4$) was observed ($d = 0.35$, 95% CI [0.13, 0.58], $p = 0.002$, $I^2 = 0\%$). No significant effect of behavioral interventions on cognitive functioning was observed ($p = 0.05$).

Discussion

The current meta-analysis synthesized data from 14 studies to examine the effects of cognitive rehabilitation programs on cognitive functioning in patients with cancer. Cognitive functioning in this meta-analysis included general neuropsychological outcomes, perceived cognitive functioning, memory, executive function, attention, and verbal ability as the primary outcomes. The results are consistent with those of previous systematic reviews, which have reported significant impairments in multiple domains of cognitive functioning, including motor function (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Falletti et al., 2005; Stewart et al., 2006), memory (Anderson-Hanley et al., 2003; Jansen et al., 2005), executive functioning (Anderson-Hanley et al., 2003; Jansen et al., 2005), verbal ability (Falletti et al., 2005; Stewart et al., 2006), and visuospatial ability (Falletti et al., 2005; Stewart et al., 2006). The results of the meta-analyses indicated that cognitive rehabilitation programs significantly improved memory ($d = 0.21$) and perceived cognitive functioning ($d = 0.41$). When the four trials in which blinding of outcome assessment did not occur were excluded (Cimprich & Ronis, 2003; Ferguson et al., 2012; Locke et al., 2008; Milbury, 2013), no significant effects on memory were noted ($d = 0.33$, $p = 0.06$). The results for perceived cognitive functioning also remained unchanged after excluding three low-quality studies (Ferguson et al., 2012; Goedendorp et al., 2014; Milbury, 2013) ($d = 0.51$, $p < 0.001$). Therefore, additional well-designed RCTs with adequate sample sizes are necessary to enable appropriate conclusions.

No effects on cognitive performance as measured by tests of attention, executive functioning, and verbal ability were observed. Consequently, the current study suggests that patients with cancer with cognitive impairment can expect slight, focused improvement in memory ability and perceived cognitive function with nonpharmacologic interventions, whereas other cognitive domains remain unaffected. The improvement in self-reported cognitive symptoms in this study is consistent with the findings of previous review studies in this field (Gehring et al., 2012). These results also are consistent with two additional

TABLE 2. Use of Objective Measures of Cognitive Functioning in Reviewed Studies (N = 14)

Measure	n	Reliability and Validity	Description
Attention			
Digit span (DSF/DSB)	4	Standardized measures	Cognitive CDA is mediated by auditory and verbal processing. The DSF, or low-demand condition, measures the number of information bits an individual can attend to at one time. The DSB, or high-demand condition, requires sustained use of CDA for performance of the mental reversing operation.
Trail Making Test (TMT)	4	Standardized measures	A standard measure of CDA requiring effective inhibition of competing response for accurate completion of the task in a timely manner. TMA and TMB are measured. TMA requires the participant to connect a series of randomly arrayed items as quickly as possible. TMB requires the participant to connect a series of 25 circles numbered 1 to 13 randomly intermixed with letters. The scores for TMA and TMB are the number of seconds required to complete the task.
Repeatable Battery of the Assessment of Neuropsychological Status (R-BANS)	2	Standardized measures	R-BANS is a brief, individually administered test completed with the patient to examine multiple areas of cognitive functioning.
Necker Cube Pattern Control (NCPC)	2	Unclear	NCPC is a newly developed test of directed attention capacity that requires active inhibition of a competing pattern stimulus. The score is the percentage reduction in pattern reversals from baseline to holding condition.
Stroop Color and Word Test (SCWT)	1	Standardized measures	The SCWT is a brief five-minute test. The SCWT measures sustained and selective visual attention by requiring patients to inhibit habitual patterns of responding and attend to atypical stimuli.
Test of Everyday Attention (TEA)	1	Standardized measures	TEA measures auditory selective attention and working memory. Elevator counting with distraction (number correct = 0–10)
Letter Digit Substitution Test (LDST)	1	Standardized measures	LDST measures attention, information processing speed, and psychomotor speed. Scores: 90 seconds of writing (number correct = 0–125)
Memory			
Rey Auditory Verbal Learning Test (RAVLT)	3	Standardized measures	RAVLT is a task of verbal memory in which participants hear a word list and must recall it after several presentations and a short delay.
Visual Verbal Learning Test (VVLTL)	2	Unclear	VVLTL measures verbal learning and memory. Trial 1 (number correct = 0–15) measures immediate verbal span. Delta (number correct = 0–15) measures verbal learning effect. Delayed recall (number correct = 0–15) measures verbal memory after an interval.
Digit symbol	2	Standardized measures	Digit symbol substitution test consists of nine digit-symbol pairs followed by a list of digits. Under each digit the participant should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time is measured.
Memory Scanning Test (MST)	1	Unclear	MST measures speed of memory processes. Subscores are slope and intercept. Slope measures time needed for memory scanning. Intercept measures time to complete non-memory stages.
Corsi Test	1	Unclear	The neuropsychological battery consisted of the Corsi Test for verbal and spatial immediate memory span.
Executive Function			
Category fluency (CF)	2	Unclear	CF is a test to objectively assess executive function. Speed and flexibility of verbal thought process and application of strategies
<i>(Continued on the next page)</i>			
CDA—capacity to direct attention			

TABLE 2. Use of Objective Measures of Cognitive Functioning in Reviewed Studies (N = 14) (Continued)

Measure	n	Reliability and Validity	Description
Executive Function (continued)			
Concept Shifting Test (CST)	1	Unclear	CST is a test to objectively assess executive function. Alternating attention
Letter Fluency (LF)	1	Unclear	LF is a test to objectively assess executive function. Speed and flexibility of verbal thought process
Behavior Rating Inventory of Executive Function (BRIEF)	1	Standardized measures	BRIEF is a standardized measure that captures views of an adult's executive functions or self-regulation in his or her everyday environment. BRIEF consists of several subscales that represent specific executive function domains composed of 75 items within nine theoretically and empirically derived clinical scales that measure various aspects of executive functioning.
Behavioural Assessment of the Dysexecutive Syndrome (BADS)	1	Unclear	BADS is a test to objectively assess executive function. Planning and priority setting
Hopkins Verbal Learning Test–Revised (HVLTR)	1	Standardized measures	The HVLTR examines downstream effects of executive function on verbal declarative memory.
Multiple Areas of Cognitive Function			
Wechsler Adult Intelligence Scale–III (WAIS-III)	2	Standardized measures	The neurocognitive battery was comprised of standard objective measures of attention, memory, and executive functions using published versions along with modified, equivalent alternate versions to control for practice effects. Measures included WAIS-III subtests digit span and digit symbol.
Repeatable Battery of the Assessment of Neuropsychological Status (R-BANS)	2	Standardized measures	R-BANS is a brief, individually administered test completed with the patient to examine multiple areas of cognitive functioning.
Mini Mental State Examination (MMSE)	1	Standardized measures	MMSE is a measure of global cognitive functioning. MMSE is divided into two sections, the first of which requires vocal responses only and covers orientation, memory, and attention. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender-Gestalt Figure.
CDA—capacity to direct attention			

studies (Ferguson et al., 2007; Von Ah et al., 2012) that were not included in this meta-analysis because of insufficient statistical data.

Cognitive rehabilitation may be a more attractive option for treatment than pharmacologic interventions among patients with cancer because rehabilitation is less invasive (Gehring et al., 2012). However, the effect size cannot be considered to be robust because the fail-safe N for perceived cognitive functioning was 5.3, which did not exceed 5N+10. That is, 5.3 trials with no significant results were required for the mean effect to be nonsignificant.

According to the subgroup analyses in four trials with 316 participants, psychological interventions (e.g., meditation, cognitive behavioral therapy) had a significant effect on self-reported cognitive functioning among patients with cancer ($d = 0.35$,

$p = 0.002$) with no statistical heterogeneity observed between study estimates ($I^2 = 0\%$). This result is consistent with the results of a meta-analysis on the well-being of patients with cancer (Zimmermann, Heinrichs, & Baucom, 2007). It has generally been observed that subjective cognitive function tends to correlate more highly with emotional distress and well-being than objective neuropsychological test performance (Cull et al., 1996; Hall, Isaac, & Harris, 2009; Middleton, Denney, Lynch, & Parmenter, 2006; Sawrie et al., 1999; Schagen et al., 2008). This finding may reflect the fact that subjective cognitive symptoms, fatigue, and mood disorders are more frequently improved than objectively assessed cognitive dysfunction, possibly related to the focused intervention on the patient's perception of the problem (Gehring et al., 2012).

The psychological interventions reviewed in this study highlight the application of compensatory strategies to minimize the impact of cognitive deficits in daily life. Psychological interventions may help to improve or prevent cognitive dysfunction by retraining cognitive capacities or by introducing compensation strategies such as focusing education on memory and attention, self-awareness training, self-regulation training, and cognitive compensatory strategies training (Gehring et al., 2012). These interventions target plasticity of the brain via restoration or reorganization of function (Miotto et al., 2013; Mora, 2013). A previous systematic review of patients with brain injury also reported strong evidence supporting the use of external memory aids to compensate for functional memory problems (Rees, Marshall, Hartridge, Mackie, & Weiser, 2007) without necessarily improving underlying memory abilities (Kennedy et al., 2008). Therefore, cognitive rehabilitation is effective in helping patients to learn and apply compensation strategies for residual cognitive limitations. However, several studies suggest that intervention also may directly improve the underlying cognitive functions (Serino et al., 2007; Stablum, Umiltà, Mazzoldi, Pastore, & Magon, 2007; Westerberg et al., 2007).

Three studies comprising eight psychological interventions in the current meta-analysis used computer-based programs for direct attention training, which was defined as the repeated stimulation of attention via graded exercises to improve the underlying neurocognitive system and attention functioning (Sohlberg et al., 2003). These studies did not observe a significant effect on cognitive functioning. A retraining program may, therefore, be more effective in mildly impaired patients when used in conjunction with external memory aids (Sohlberg et al., 2003).

In the current meta-analysis, cognitive rehabilitation programs had no effect on cognitive performance as measured by tests of attention, executive functioning, and verbal ability. This result is not consistent with the results of systematic reviews in patients with traumatic brain injury, which report substantial evidence supporting the positive effects of neuropsychological rehabilitation interventions on attention, memory, and executive function (Cicerone et al., 2011). Several reasons may exist as to why a significant effect was not observed in the current study. The overall recovery process after chemotherapy may have taken place, in terms of cognitive and physical condition. In addition, the low cutoff for the selection of patients with cognitive deficits may have contributed to the null finding (Poppelreuter et al., 2009). Seven reviewed studies did not report their selection criterion for patients with cognitive deficits. However, given that the studies were designed to treat patients

with cognitive impairment, the presence of objective cognitive deficits would be considered the most important selection criterion for investigators to be able to measure the effect of an intervention (Gehring et al., 2012). In addition, it may be appropriate to screen for self-reported cognitive complaints, because the experience of cognitive symptoms may be crucial in motivating patients to adhere to time-consuming cognitive rehabilitation programs (Gehring et al., 2012).

The lack of long-term follow-up assessments also may have contributed to the null findings in this meta-analysis. It has been suggested that patients may require more time to integrate learned strategies into their daily routine. Six studies in this analysis included only one follow-up assessment after the intervention. Given that the possibility of a delayed intervention effect remains unknown, future studies may include such assessments to document information regarding the persistence of potentially beneficial intervention effects (Gehring et al., 2009; Winkens, Van Heugten, Wade, Habets, & Fasotti, 2009).

In the authors' subgroup analyses, only three studies tested a behavioral intervention, and no significant effect on overall cognitive functioning was observed. The effect of physical activity on cognitive impairment in patients with cancer is a current area of interest, based on findings that physical exercise may have a positive effect on delaying or ameliorating cognitive deficits in older adults with or without cognitive decline (Day et al., 2014). Exercise has been associated with increased cerebral blood flow, hippocampal neurogenesis, changes in neurotransmitter release, increased arousal levels, and brain structures (Gligoroska & Manchevska, 2012). However, the physical activities described in this study do not necessarily represent physically demanding exercises, but rather activities such as walking in the natural environment, tending to plants, or engaging in gentle movements. When meta-analyses contain a small number of studies, the results and estimated effect sizes can be imprecise (Higgins & Green, 2011). Additional RCTs of physical exercise with adequate sample size are needed to enable the drawing of appropriate conclusions.

Limitations

In the current study, some relevant data could have been overlooked because the authors were not able to access international unpublished research and non-English based studies. Because nonpharmacologic interventions are so diverse, investigators had to provide specific information regarding (a) the degree of the patient's cognitive impairment as well as the quality, focus, and long-term assessment of the intervention and (b) medical treatments and other

Knowledge Translation

- Cognitive rehabilitation programs (psychological approach) have a positive impact on perceived cognitive functioning and memory in patients with cancer who undergo chemotherapy.
- Interventions are more effective when delivered with education, compensation strategy, and retraining.
- Cognitive rehabilitation may be a more attractive treatment option than pharmacologic intervention for chemotherapy-related cognitive decline because it is less invasive.

interventions used during and after the intervention period. The methodologic quality of the included studies was another limitation of this meta-analysis. Blinding is a critical feature of the RCT methodology design, but because of the practicalities of psychological interventions, blinding was challenging to apply in these studies. Finally, the use of small sample sizes in many studies resulted in insufficient power to detect effects of the cognitive rehabilitation program on the outcomes.

Implications for Practice and Research

A significant number of patients with cancer who are treated with chemotherapy experience cognitive decline, which negatively affects their quality of life. Nurses need to be aware of the evidence-based interventions for this potentially debilitating side effect (Von Ah, Jansen, Allen, Schiavone, & Wulff, 2011). This meta-analysis was focused on nonpharmacologic interventions, which were divided into two intervention categories: psychological and behavioral. Psychological interventions included strategies as well as education and retraining, which was administered primarily via computer-based programs. The behavioral intervention method involves activities thought to be particularly helpful in ameliorating and restoring cognitive functioning (Cimprich, 1993), such as walking in the natural environment, tending to plants, or engaging in gentle movement. The findings of this meta-analysis support the positive effects of nonpharmacologic interventions on memory and self-reported cognitive functioning. However, the current review revealed a significant effect only on the psychological intervention when the intervention types were administered separately. These psychological interventions were more effective when strategies such as focusing on education regarding memory and attention, self-awareness training, self-regulation training, and cognitive retraining were applied using an integrated approach. Behavioral interventions included in this

study were not physically demanding exercises, and there were relatively few studies with small sample sizes. Therefore, more research is needed to develop and refine behavioral interventions, such as physical exercise programs. To accomplish this, researchers will need to continue to investigate the underlying physiological mechanisms and treatment- or disease-related factors associated with cognitive impairment. Because the current study suggests that cognitive function would be most improved in patients with cancer when a mixed-intervention approach (compensation, education, retraining, and physical activity) is employed, additional research is needed.

Although the meta-analyses included studies with well-validated tools to test cognitive function, several questions remain. For example, the addition of findings from neuroimaging, such as magnetic resonance imaging, may provide a better understanding of the clinical benefits of nonpharmacologic interventions.

Conclusion

Despite some limitations, the current meta-analysis can tentatively conclude that nonpharmacologic interventions result in a small improvement in memory ability and perceived cognitive functioning among patients with cancer with cognitive impairment. However, most of the reviewed studies did not provide sufficient evidence for an effect of the cognitive rehabilitation program on cognitive performance as measured by objective tests of attention, executive functioning, and verbal ability. Therefore, additional studies on these cognitive outcomes are needed.

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