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Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial

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Abstract

Objective—To evaluate the efficacy of a brief cognitive-behavioral therapy (CBT) that is being developed for management of cognitive dysfunction following chemotherapy among breast cancer survivors. Memory and Attention Adaptation Training (MAAT) is a brief CBT designed to improve the quality of life and function among cancer survivors with post-chemotherapy cognitive complaints.

Methods—An initial, two-group (MAAT versus waitlist, no treatment control), randomized clinical trial (RCT) was conducted. Forty stage I and II female breast cancer survivors (mean age = 50; SD = 6.4) were randomized to conditions and assessed at baseline, post-treatment (8 weeks) and 2-month follow-up assessment points on measures of: (1) self-reported daily cognitive failures; (2) quality of life; and (3) neuropsychological performance. Participants were also assessed for satisfaction with MAAT.

Results—With education and IQ as covariates, MAAT participants made significant improvements relative to controls on the spiritual well-being subscale of the quality of life measure and on verbal memory, but statistical significance was not achieved on self-report of daily cognitive complaints. However, moderate-to-large effect sizes were observed on these outcomes. Participants gave MAAT high satisfaction ratings.

Conclusions—Although this initial RCT is a small study, MAAT participants appear to improve on one measure of quality of life and verbal memory performance relative to no treatment controls and rate MAAT with high satisfaction. These data are encouraging and support the continued development and evaluation of MAAT efficacy.

Keywords

breast cancer; chemotherapy; cognitive dysfunction; cognitive-behavioral therapy; survivorship

Introduction

Cognitive dysfunction associated with cancer chemotherapy has gained increased research attention over the last 2 decades [1–4]. Broad findings within this body of work are: (1) cognitive impairment is detected in 17–75% of chemotherapy recipients with most deficits found to be in mild-to-moderate ranges [2,5–7]; (2) neuropsychological domains most affected appear to be verbal working memory, psychomotor processing speed, and visual-spatial memory; and (3) cognitive impairment is found in cancer survivors years after completing chemotherapy in contrast to survivors of the same cancer type who did not receive chemotherapy [2,8,9]. Overall, the problem of cognitive dysfunction associated with chemotherapy appears to affect a large portion of individuals and for periods well beyond treatment completion.

Although much research on chemotherapy-related cognitive change has been performed, many questions remain. For example, variability in prevalence estimates has much to do with differences among investigators' definition of cognitive impairment and neuropsychological testing methods used [3]. Moreover, mechanisms of how anti-neoplastic agents exert changes in cognitive function have yet to be elucidated, though functional MRI studies and animal models are suggesting candidate processes [10–13]. As research continues to address these knowledge gaps, both empirical and qualitative data have documented the negative functional impact on survivors [14,15]. Many individuals report cognitive problems have the greatest deleterious effects when resuming functional roles in the family, community, and workplace after treatment. There are reports of individuals who have had to delay or defer educational pursuits, switch employment positions with less responsibility and/or pay, leave employment, or withdraw from valued social activity for fear of appearing cognitively impaired [4,16,17]. Addressing the functional impact of this problem among cancer survivors is a long-standing priority of the President's Cancer Panel [18] and is an important part of comprehensive cancer care [19].

A number of treatment strategies addressing the problem have been tested. Two early randomized, placebo-controlled drug trials, one with dexamethylphenidate [20] and the other with modafinil [21], have demonstrated gains in neuropsychological test scores for participants. However, over 40% of patients in the dexamethylphenidate trial reported problematic headache and over 26% reported nausea. In the modafinil trial, gains were observed for participants only 4 weeks after chemotherapy but individuals with long-standing cognitive problems were not studied. Neither trial studied treatment effects on daily function. Therefore, in light of a poor understanding of the etiology of cognitive effects of chemotherapy and potential for medication side effects, continued development of non-pharmacological approaches can offer survivors lower risk alternatives with an emphasis on functional improvement.

Memory and Attention Adaptation Training (MAAT) is a brief cognitive-behavioral approach designed to help cancer survivors learn and apply adaptive strategies to reduce the negative functional and quality of life impact of cognitive problems [16]. Rather than emphasizing a traditional cognitive rehabilitation approach of 'mental exercise', MAAT emphasizes the acquisition of compensatory strategies to reduce the incidence and impact of cognitive failures on daily activity [22,23]. The distinction between cognitive training and compensatory strategy approaches is discussed in reviews of cognitive rehabilitation research [24,25]. A cognitive training approach assumes that repetitive training on cognitive tasks, such as those that involve visual-motor processing speed, can spawn repair of damaged neuro-circuitry to recover memory function. In contrast, a compensatory strategy approach emphasizes acquisition of new behaviors and cognition to compensate for chronic memory dysfunction; that is, the learning of new procedures to complete daily tasks *for*

which memory is required. In general, research on cognitive effects of chemotherapy demonstrates little to no correspondence between report of memory dysfunction and objective neuropsychological test performance [26,27]. It may be that interventions for chemotherapy-related cognitive dysfunction will be most effective with a focus on quality of life improvement, which is the emphasis of MAAT. At the same time, some researchers postulate that the physiological substrates of compensatory strategy approaches involve recruitment of healthy or undamaged cortical or subcortical structures that enable individuals to achieve pre-injury task performance [11,25]. Therefore, compensatory strategy approaches may improve neuropsychological test performance in domains targeted by compensatory strategies and improve overall quality of life.

MAAT is brief with four office visits and telephone follow-ups designed to help survivors generalize compensatory strategies smoothly into daily routines (e.g. consistent, efficient use of a day planner or activity schedule). A one-group pilot study demonstrated MAAT reduced self-reported cognitive problems at post-treatment, 2-month and 6-month follow-up assessments. A mild increase was found on a quality of life measure, and gains were also observed in verbal memory and processing speed. Participants reported overall high treatment satisfaction [16]. In short, breast cancer chemotherapy recipients reported improvements in quality of life, self-reported cognitive symptoms and improvements in neuropsychological test performance. However, there was no control group to evaluate efficacy of MAAT over time with respect to improvement in daily cognitive complaints, and neuropsychological test performance gains could simply have been due to effects of repeat administration. Therefore, the current study presents results from a waitlist, randomized clinical trial (RCT) to address these concerns. MAAT continues to be under development and this report presents data on the current version in order to guide future modifications. In this RCT, we hypothesized that:

- (1) Participants enrolled in MAAT would report fewer daily cognitive problems than controls at post-treatment assessments.
- (2) Participants enrolled in MAAT would report improved quality of life compared with controls at post-treatment assessments.
- (3) Participants in MAAT would demonstrate significant improvement in neuropsychological test performance compared with controls at post-treatment assessments.
- (4) MAAT participants would rate MAAT with high satisfaction.

Methods

Participants

Forty adult female breast cancer survivors who received adjuvant chemotherapy for stage I and II breast cancer were recruited for the study through letters asking for volunteers mailed to survivors from the Comprehensive Breast Program at Dartmouth-Hitchcock Medical Center. Newspaper advertisement and fliers posted at other medical oncology offices were also used. All recruitment procedures were approved and overseen by Dartmouth College's Committee for the Protection of Human Subjects. Potential participants who called the investigation team were scheduled for a phone interview that addressed inclusion and exclusion criteria. Oral consent was obtained prior to the telephone screening procedures followed by standard questions to determine eligibility in addition to screening with the Primary Care Evaluation of Mental Disorders (PRIME-MD). The PRIME-MD is a brief, semi-structured clinical interview designed for rapid identification of mental disorders in primary care settings [28]. Inclusion criteria were: (1) diagnosis of stage I or II breast

cancer; (2) at least 18 months post-treatment currently disease free (not excluding individuals on hormonal therapies such as selective estrogen receptor modulators or aromatase inhibitors); (3) treatment involved standard dose adjuvant chemotherapy; (4) complaint of memory and attention problems following chemotherapy; (5) able to speak and read English; (6) at least 18 years of age at diagnosis and able to provide informed written consent. Exclusion criteria were: (1) history of CNS disease; (2) history of CNS radiation, intrathecal therapy or CNS-involved surgery; (3) neuro-behavioral risk factors such as traumatic brain injury, history of neurological disorder, learning disability or substance addiction; (4) current psychiatric disorder. Breast cancer surgery and non-CNS radiation were not exclusionary criteria. To identify women who met the inclusion criterion for chemotherapy cognitive complaints, each was required to answer in the affirmative: 'do you have problems with memory and attention since having chemotherapy, and do you believe chemotherapy contributed to the problems?' Other inclusion/exclusion criteria (e.g. breast cancer diagnosis, non-CNS disease and type of chemotherapy, etc.) were later verified with medical chart review. The decision to include individuals 18 months post-chemotherapy was based on the finding that acute effects of stress, depressive symptoms, anxiety, and chemotherapy recovery occur within 6 months of treatment completion. Therefore, we wanted to control for these acute recovery effects [2,29–31].

Procedure

Participants completed baseline assessment of self-report measures and a brief neuropsychological battery before being randomized to treatment and waitlist conditions using computer generated assignment. The research assistant completing all assessment and testing was blind to participant group membership. Nineteen participants were randomized to treatment (MAAT), while 21 were randomized to waitlist control. Those participants randomized to waitlist were assessed 2 months following baseline to approximate duration of MAAT completion (8 weeks). Three participants dropped out of the study citing travel inconveniences, personal reasons, or relocation prior to the post-treatment assessment. Two additional participants dropped out prior to the 2-month follow-up assessment (see Figure 1). These participants did not differ significantly from the final sample demographic or dependent variables.

Intervention—MAAT is a brief cognitive-behavioral therapy (CBT) aimed at enhancing cancer survivor skills for self-managing and coping with cognitive failures of daily life. The version of MAAT in this study consisted of four biweekly individual office visits 30–50 min in duration with phone contacts between visits. In each visit, participants reviewed present findings and knowledge about cognitive effects of chemotherapy, learned how to self-monitor and identify 'at-risk' situations where cognitive failures are likely to occur (self-awareness training), and learned and rehearsed compensatory strategies to prevent or lessen negative consequences of cognitive failure (e.g. emotional distress or daily occupational or social role performance). Participants applied the strategies in daily situations to foster adaptive learning and telephone contacts between visits were intended to reinforce use of new behaviors or modify the strategy to enhance effectiveness.

There are four cognitive-behavioral components to MAAT: (1) Education of memory and attention, what 'normal' cognitive failures are and apparent effects of chemotherapy on memory function; (2) self-awareness training to identify 'at-risk' situations where cognitive failures are likely to occur; (3) self-regulation training emphasizing applied relaxation training and stress management with activity scheduling and pacing; (4) cognitive compensatory strategy training. Examples of compensatory strategies include: Self-Instructional Training (SIT) [32], or covert verbal self-guidance to enhance procedural memory and focused attention, verbal rehearsal, using a day planner, external cueing, and

visualization strategies. Each participant received a MAAT workbook with detailed descriptions of compensatory strategies, educational material, and guides on how to apply compensatory strategies. The clinician for MAAT follows a detailed clinician's manual to enhance treatment fidelity. All treatment was conducted by one clinician (R. F.) who was blind to all participant test performance. It was impossible to blind the clinician to the treatment or control assignments, but, as noted above, the research assistant who conducted assessments for all participants was blind to participant randomization. Participants were instructed not to reveal their group assignment either verbally or non-verbally (e.g. inadvertently carry the MAAT workbook in view of the assistant or discuss MAAT).

Research design—The primary research design was a 2 (Group: MAAT versus waitlist) $\times$ 3 (Time: baseline, post-treatment, 2-month follow-up) factorial repeated measures model. The principal dependent measures were self-reported cognitive problems of daily life, breast cancer quality of life, and a brief battery of standardized neuropsychological tests evaluating verbal memory and visual-motor processing speed.

Measures—Self-report measures included:

- (1) *Multiple Ability Self-Report Questionnaire (MASQ)* [33]. The MASQ is a 48-item self-report measure of problems of daily cognitive function across five neurocognitive domains: language, visuo-perceptual, verbal memory, visual memory, and attention. Respondents are asked to rate how frequently they have a particular cognitive problem on a 5-point scale from 'Almost Never' to 'Almost Always'. Lower scores represent fewer cognitive complaints.
- (2) *Quality of Life—Cancer Survivors (QOL-CS)* [34]. The QOL-CS is a 41-item self-report rating scale that assesses four domains of quality of life (physical, psychological, social and spiritual) on an 11-point scale, where 0 represents the worst possible outcome and 10 the best possible outcome. There is strong evidence for validity and reliability [35].
- (3) *Center for Epidemiological Study—Depression (CES-D)* [36]. The CES-D is a 20-item measure of depressive symptoms widely used in epidemiological and clinical research. Patients are asked to rate how frequently they have experienced each symptom over the past week on a four-point scale. The CES-D has strong data supporting its validity and reliability [37].
- (4) *Spielberger State-Trait Anxiety Inventory (STAI)* [38]. The STAI contains two 20-item forms, which measure state anxiety (the level of current anxiety) and trait anxiety (the general level of anxiety experienced). Extensive data on reliability and validity support the utility of the measure.
- (5) *Treatment Satisfaction*. All participants completing MAAT rated how satisfied they were with treatment results on a 9-point (0–8) Likert-type rating scale. Participants rated how satisfied they were in general with the program using the verbal anchors 'not at all satisfied'(0) to 'completely satisfied' (8). Participants were asked to rate how helpful MAAT was in *improving* problems with memory and attention, and how helpful MAAT was in enabling them to *compensate* for memory and attention problems. Both items are rated on the same 0–8 scale with verbal anchors 'not at all helpful' (0) to 'completely helpful' (8). Finally, participants completing MAAT were asked to rate how helpful individual compensatory strategies were for dealing with daily problems of memory and attention. Five-point Likert-type ratings were used with the anchors 'not at all helpful'(0) to 'completely helpful' (4).

Neuropsychological tests used in this study were selected on the basis of previous cancer survivor research that demonstrated statistical discrimination between survivors treated with chemotherapy versus not receiving chemotherapy [39]. Two domains of neuropsychological functioning were represented: verbal memory and processing speed. For verbal memory assessment, the total score of the California Verbal Learning Test-2 (CVLT-II) [40] was used. This involved the total raw score across trials 1–5. Alternate forms (standard form, alternate form) were used to minimize practice effects. In addition, participants received different sequencing of alternate forms across the baseline, post-treatment, and follow-up time points to minimize order effects between participants. That is, some participants received a 'standard form, alternate form, standard form' CVLT-II sequence, while others received an 'alternate form, standard form, alternate form' sequence. For processing speed, the Trail Making Number-Letter Trial, Color-Word-Interference, Color-Word and Switching Trials from The Delis-Kaplan Executive Function System (D-KEFS) [41] and the Digit Symbol-Coding subtest from the Wechsler Adult Intelligence Scale-III [42] were used.

Analytic procedure—Sample size for this early phase RCT was based on effect sizes from pilot data previously published [16] and power tables recommended by Cohen [43]. Statistical power was projected at 0.80 with n of 20 per group with alpha at 0.05 for the two-group, repeated measures design.

The first step in analyses was to account for missing data using linear interpolation. In short, linear interpolation methods replace missing data points with predicted values based on patterns in an individual participant's previous scores and group membership [44]. This was performed to compensate for unequal group sizes through all post-treatment assessment time points, maintain power, and glean the best possible estimates of treatment effect using a small sample with the limited budget of this initial RCT. The use of linear interpolation was to account for missing data from a total of five participant dropouts over the course of trial participation; three at post-treatment, two at 2-month follow-up (see Figure 1). The overall attrition rate was only 12.5% (5 of 40 participants), which is an improvement over a 19% attrition rate in previous MAAT research [16] and is better than an average 23% attrition rate of CBT trials in anxiety disorders research [45]. Although not ideal, the use of linear interpolation enabled us to fairly evaluate MAAT effects in this limited sample with a relatively small amount of missing data. Specific numbers of participants who dropped out of the study at the post-treatment assessment point were 1 (out of 19) in the treatment group and 2 (out of 21) in the waitlist control group (see Figure 1). At the 2-month follow-up assessment point, one additional participant dropped out of each group leaving a total of two participant dropouts of 19 in the treatment (MAAT) condition and three of 21 participants in the waitlist control condition.

Following linear interpolation, all variables were evaluated for distribution characteristics. All were found to be normally distributed. Correlation analyses revealed that years of education and estimated IQ based on demographic variables [46] were significantly correlated with primary outcome measures (ranges of $r = 0.26$ to 0.55). Therefore, to test the main hypothesis, repeated measures analysis of covariance was used with full scale IQ and years of education as covariates.

Within group effect sizes were calculated using Cohen's d to determine the effects of treatment across baseline to post-treatment and baseline to 2-month follow-up comparisons. This was carried out for both MAAT and waitlist groups [47]. Differences in effect sizes between groups were calculated by subtracting the control group effect size from the treatment group to account for (or 'extract' the effect of) factors that could influence improvement or decline in control group dependent variables as suggested by Rohling *et al.* [24]. Such factors influencing waitlist control outcomes may include practice effects of

repeat exposure to neuropsychological tests, spontaneous recovery of cognitive symptoms, or increased attention for participating in a study on cognitive effects of chemotherapy.

Results

Over 100 women made inquiries about study participation. Fifty-three breast cancer survivors agreed to be screened for eligibility via telephone. A total of 45 women screened via telephone met eligibility and were scheduled to undergo baseline assessment. A total of 41 women were enrolled (see Figure 1). One participant dropped out after baseline assessment and prior to randomization.

The majority of participants were Caucasian with 2.5% of the sample representing other ethnic groups, reflecting demographic characteristics of northern New England. The mean age of the entire sample was 50.3 (SD=6.4) with an average of 16.4 (SD=2.4) years of education and an estimated mean full scale IQ of 114.72 (SD=4.2) based on demographic and educational factors [46]. Participants randomized to treatment or waitlist did not differ on these variables (Table 1). The final sample had a range of adjuvant chemotherapy regimens that included variations of cyclophosphamide/methotrexate or cyclophosphamide/doxorubicin in addition to 5-fluorouracil among other compounds (e.g. AC and CAF). All participants were postmenopausal at enrollment. Twelve individuals in the waitlist group and 11 enrolled in MAAT (30% and 27.5% of the entire sample, respectively) were taking hormonal therapies. Chi-square analyses indicated that these proportions did not differ over the course of the study. Eighteen participants (45%) were taking antidepressant medications although no participant met diagnostic criteria for major depressive disorder. Seventeen individuals (42.5%) were taking antidepressant medications at the post-treatment assessment point with 15 on these medications at post-treatment (2 months after baseline). Chi-square analysis indicated no differences between MAAT and waitlist control participants in proportion of individuals taking antidepressant medications at any assessment point.

Daily cognitive problems—MASQ total score

Controlling for years of education and IQ, a significant time effect for both MAAT and waitlist control participants was observed in MASQ total score (see Table 2). However, the group by time interaction did not reach statistical significance $F(2, 76)=1.24, p=.30$. As expected, moderate-to-large effect sizes were obtained in the MAAT group with much smaller effect sizes in the waitlist condition at post-treatment and 2-month follow-up (Table 2). MASQ data showed baseline difference in mean MASQ total score for MAAT participants ($M=120.05$; $SD=21.42$) compared with controls ($M=111.90$; $SD=28.01$). However, this difference was not significant and therefore was not used as a covariate in MASQ analyses.

Quality of life—QOL-CS

The only scale on the QOL-CS that demonstrated a significant group by time interaction effect (with education and IQ as covariates) was the spiritual well-being subscale $F(2, 76)=3.44, p<0.05$. Planned comparisons identified significant differences at the post-treatment and 2-month follow-up time point over baseline for the MAAT group ($p=0.03$) but not the waitlist group. Cohen's d demonstrated moderate effect sizes in the MAAT participants compared with waitlist controls (Table 2). No statistically significant changes were observed in depression or anxiety scores over time for either MAAT or waitlist participants, likely owing to the fact that all participants enrolled were screened for problematic depression or anxiety and thus had low baseline scores.

Neuropsychological test results

Controlling for education and IQ, one group by time interaction attained statistical significance for neuropsychological outcomes. MAAT participants demonstrated improvement in CVLT-II total score (verbal memory) relative to waitlist controls over time $F(2, 76)=3.16, p<0.05$. Planned comparisons indicated MAAT participants made significant gains over baseline at both post-treatment and 2-month follow-up ($p<0.001$). Effect sizes for MAAT participants were larger than that of wait-list controls for baseline to post-treatment and baseline to 2-month follow-up differences.

In contrast to verbal memory outcomes, no significant group by time interactions on any of the processing speed neuropsychological measures were observed. Effect sizes in both the MAAT and waitlist control groups were roughly equivalent as evidenced by small treatment-control group differences in effect size for all processing speed outcomes (See Table 2).

Treatment satisfaction

Fifteen participants completed MAAT satisfaction ratings and reported high general satisfaction with a mean of 7.0 (SD=1.05; 0=not at all satisfied; 8=completely satisfied). As expected, participants rated MAAT lower with regard to *improving* memory ($M=5.2$; SD=1.59), in contrast to rating MAAT higher for *compensating* for daily memory failures ($M=6.7$; SD=1.54; where 0=not at all helpful; 8=completely helpful).

Analyses completed to examine participants' ranking of helpfulness of the various compensatory strategies used in MAAT indicated the top five rated strategies included: applied relaxation methods (self-regulation, arousal reduction), using a schedule or day planner/organizer, verbal rehearsal methods, activity pacing and scheduling, and SIT.

Discussion

Breast cancer survivors who underwent MAAT made improvements on the spiritual well-being subscale of the QOL-CS and verbal memory (CVLT-II, total score) relative to survivors assigned to a waitlist condition, controlling for IQ, and years of education. Although moderate in magnitude, these outcomes are positive and provide some added support for MAAT efficacy at this early stage of intervention development. The QOL outcome may be explained by the item content of the QOL-CS spiritual well-being subscale. Of the seven items comprising the subscale, four involve content of being positive, hopefulness, purpose in life, and certainty about the future. The spiritual well-being subscale may therefore reflect an optimistic or more positive survivorship outlook among MAAT participants at post-treatment. One intended effect of MAAT is to enhance coping with cognitive problems despite their persistence and the present result may reflect such an outcome. By contrast, social, physical, and other subscales of the QOL-CS may not be responsive as targets of the MAAT intervention.

The improvement in CVLT-II total score relative to controls over time suggests MAAT may help participants to improve verbal memory performance. This was not expected as a primary outcome but the moderate-to-large effect size difference between MAAT and control participants (see Table 2) suggests this result is beyond expected effects of repeat CVLT-II administration or practice. This result is highly encouraging since mild verbal memory decline is a consistent finding in research on post-chemotherapy-related cognitive change [4,9,39,48,49]. It remains unclear if the compensatory strategy component of MAAT has a direct effect on verbal memory performance or if other components of MAAT (e.g. applied relaxation and arousal reduction) contribute to test performance enhancement.

Interestingly, none of the processing speed neuropsychological measures were observed to significantly improve among MAAT participants relative to waitlist controls. It may be that MAAT compensatory skills and other components are targeting verbal memory and thus do not affect speed of cognitive or psychomotor processing. Indeed, SIT and verbal rehearsal are examples of MAAT compensatory strategies that involve vocalization during task performance. Further investigation of MAAT effects on CVLT-II performance in larger samples with secondary analysis of individual MAAT components may answer questions about the mechanism of this MAAT effect.

It was hypothesized that MAAT participants would demonstrate significantly fewer self-reported daily cognitive problems following treatment compared with waitlist participants. Statistical significance was not achieved over post-treatment or follow-up assessment points on this measure (MASQ total score). However, larger effect sizes were observed within the MAAT condition on MASQ total score compared with waitlist controls (Table 2), suggesting some MAAT effect over and above MASQ score reductions observed in controls. This result may not have reached statistical significance due to the small sample size and the study being underpowered. As with other self-report measures of daily cognitive complaints, the MASQ total score in our sample did not correlate significantly with any neuropsychological test scores. This result is similar to other studies of chemotherapy recipients [39,50,51] where there is typically no correspondence between neuropsychological test performance and self-report of daily cognitive complaints. Overall, results of this small RCT suggest that MAAT as a CBT approach may help to improve breast cancer quality of life and verbal memory performance.

An alternative interpretation of these results is that MAAT is ineffective and treatment effects are short-lived. The sample size was small and linear interpolation methods were used to account for missing data, thus potentially producing type-I error inflation. However, though underpowered, this trial did produce moderate effect sizes that lend some support for MAAT as viable treatment for chemotherapy-related cognitive change. A comparison to contemporary literature supports this standpoint. For instance, in cancer survivorship literature, present results are similar to a recent report of a much larger ($n=52$ per group), waitlist controlled and comprehensive cognitive rehabilitation trial for children and adolescents with CNS cancer or CNS-involved treatment [47]. In that study, 161 children, ranging in age from 6–17 years (mean age about 11 years), were enrolled across six research sites. With multiple neuropsychological test outcomes along with self-report and parent/teacher ratings, only academic achievement was found to attain statistical significance in treatment versus control participants over time. This was one of six standardized test composite scores used as primary neuropsychological outcomes. Similarly, two of five functional measures (Conners' Rating Scales assessing parent ratings of child attention and on-task behavior, respectively) achieved statistically significant improvement in treatment versus control conditions over time. Effect sizes in these three statistically significant results were 0.19 for achievement, -0.48 for attention, and -0.45 for on-task behavior. Each of these effect sizes was calculated for only the baseline-to-post-treatment differences. Therefore, while the current RCT of MAAT only achieved statistical significance on two outcome measures (one quality of life and one neuropsychological measure), the effect sizes seen in Table 2 of the current report were comparable in magnitude reported by Butler *et al.* [52]. Further, while our principal measure of daily cognitive problems (MASQ total score) did not attain a statistically significant outcome, effect size reported in this smaller trial for adults is 0.43—comparable to Butler *et al.*'s results with a more intensive pediatric treatment.

It could also be argued that linear interpolation used at post-treatment and 2-month follow-up time points was not 'true' data and thus results presented were inaccurate. However, in

examination of non-interpolated data on the two outcome measures that achieved statistical significance, means and standard deviations were highly similar to interpolated data. For instance, the non-interpolated post-treatment follow-up means for MAAT participants on the QOL-CS Spiritual subscale were 6.49 and 6.10, respectively, while the interpolated means were 6.57 and 6.14 (as seen in Table 2); for the waitlist group, the non-interpolated means were 5.99 and 5.92, respectively, whereas the interpolated means were 6.02 and 6.02, respectively (see Table 2). This resulted in an even larger effect size difference between groups (-0.28) at the 2-month follow-up. Similar results were seen in the CVLT-II effect size difference at 2-month follow-up (-0.67 compared with -0.63 seen in Table 2) and with the MASQ outcomes at 2-month follow-up (0.33 compared with 0.27 in Table 2). Therefore, we believe linear interpolation allowed for good estimates of missing data in order that statistical significance testing could be accomplished. If anything, it may have lead to slight underestimates of effect size. Linear interpolation is not a perfect method of dealing with data missing due to attrition in clinical trials, but given the costs in time and monetary expense in research on treatments for this survivorship problem, we believe the method allowed for the best evaluation of available data in the development of MAAT. A more complete discussion can be seen by Twisk [53].

With respect to the broader cognitive rehabilitation literature, the present results appear promising for MAAT. Effect size interpretation is best done in the context of a body of treatment literature to determine the meaningfulness of between group differences in an intervention study [54]. In a recent meta-analysis published by Rohling *et al.* [24], global effect sizes calculated across a broad set of cognitive rehabilitation methods for various brain injured populations ranged 0.25 – 0.34 . The effect sizes reported at post-treatment and follow-up time points for our primary neuropsychological outcome measure, CVLT-II total score (-0.50 and -0.63 , respectively) are much larger than those reported in Rohling *et al.* In summary, in the context of literature of cognitive rehabilitation interventions in cancer survivors and the broader brain injury population, results of this small RCT of MAAT appear comparable in effect size outcomes. From this perspective, we assert that further development and research on MAAT efficacy is justified given the needs of a growing adult cancer survivor population [55].

Several limitations of the present study should be addressed in future research. First, obtaining a larger sample and intensifying MAAT by expanding the number of treatment sessions would likely yield increased power and help to determine more robust conclusions about MAAT efficacy. Modification of MAAT in this respect is underway, and a larger RCT with active control condition is planned. The goal is to construct and carry out a large enough study so that linear interpolation can be avoided and sufficient power can be gleaned to increase confidence in primary outcomes. Use of contemporary statistical methods such as multilevel modeling is less sensitive to participant attrition and missing data in clinical trials and avoids violations of assumptions in MANOVA methods [56]. In addition, an active control condition, such as supportive psychotherapy, can determine if the effects of MAAT are or are not attributable to common psychotherapy factors such as attention, social support, or conveyance of empathy.

A second limitation of the present study has to do with the primary self-report measures used. Several points should be made here. First, it may be that the MASQ and the QOL-CS are not precisely measuring the quality of life targets of MAAT. As a CBT, MAAT is intended to enhance adaptive behaviors and cognitions to improve the overall function and quality of life despite cognitive problems. The MASQ does not assess the *impact* on quality of life that cognitive dysfunction can produce—it only assesses subjective report of daily cognitive complaints. Likewise, the quality of life instrument used in the present research, the QOL-CS scale, has only one item pertaining to cognitive function. Therefore, these

measures may not precisely measure intended MAAT outcomes. At the time of early MAAT development and start-up of this RCT, there was no available self-report measure of quality of life impact of cancer treatment-related cognitive problems. Fortunately, that has changed. The Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog) has been developed with breast cancer survivors who have undergone chemotherapy [57,58]. This measure appears to be sensitive to change and thus may be a better measure of quality of life impact of MAAT. Using the FACT-Cog as a primary dependent measure, in future MAAT research may be a more accurate assessment of MAAT efficacy.

A second point about using the MASQ has to do with whether our sample of breast cancer survivors reported few cognitive complaints when enrolled, such that a statistically significant reduction in MASQ total score in MAAT participants did not occur due to already low symptom report. In fact, our sample registered much higher MASQ total scores at baseline (reported more daily cognitive complaints) compared with a healthy control sample reported by Ahles *et al.* (MASQ total score, $M = 85.9$; $SD = 17.9$). Therefore, this 'floor effect' does not explain present results. It may also be that the MASQ is not sensitive to change over time. However, recent data by Ahles *et al.* [59] suggest the MASQ is sensitive to change where increases in MASQ total score from pre-chemotherapy to post-chemotherapy were observed among chemotherapy recipients. The investigators also found that matched cancer patients who did not receive chemotherapy and healthy controls did not produce higher MASQ scores over time. Thus, the MASQ may have reasonable sensitivity to change characteristics in the breast cancer population. On the whole, these results and the moderate-to-strong MASQ total score effect sizes seen in Table 2 suggest that statistical significance was likely not achieved due to a small sample size and low power, not poor psychometric properties of the MASQ.

A third limitation of current findings is that our sample consisted of female breast cancer survivors and it is unknown if male cancer survivors with chemotherapy-related cognitive dysfunction would respond favorably to MAAT. In addition, our sample of women consisted of high functioning individuals with an average educational level roughly equivalent to a bachelor's degree who were primarily rural and Caucasian. All participants were screened for anxiety and depression and thus had low levels of these symptoms upon enrollment. This may not be reflective of clinical populations where more distress with cognitive complaints may be present. Perhaps MAAT has its greatest clinical effects with individuals reporting more distress than the current sample. Evaluating MAAT in more diverse samples across varying levels of emotional distress, cancer diagnoses, gender, educational, and demographic factors is needed. Finally, MAAT was conducted by only one clinician in this early phase RCT. Efficacy research using multiple clinicians is needed to determine the magnitude of clinician effects on outcomes and whether MAAT can be readily learned and administered by differing clinicians. In conclusion, MAAT research and development should continue taking into consideration these points of research quality improvement.

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Figure 1.
Study flowchart. *Note:* MAAT=Memory and Attention Adaptation Training

Table 1

Background characteristics of participants

<i>Variable</i>	Group		
	Total (n=40)	MAAT (n=19)	Waitlist (n=21)
Age	50.28 (6.4)	51.21 (7.3)	49.43 (5.1)
Education (in years)	16.38 (2.4)	16.95 (1.9)	15.86 (2.7)
Estimated IQ	114.72 (4.2)	115.61 (4.1)	113.92 (4.1)
Marital status			
Currently married		76.2%	63.2%
Caucasian	97.5%		
Other	2.5%		

Note: No factor was significantly different between groups ($p>0.05$).

Table 2

Group comparisons of principal outcomes

	Baseline Mean (SD)	Post-Tx Mean (SD)	<i>D</i>	2-Month f/u Mean (SD)	<i>d</i>	<i>F</i>	<i>p</i>
Functional/quality of life outcomes							
MASQ total score ^a							
Treatment <i>n</i> =19	120.05 (21.42)	107.03 (17.25)	0.67	108.95 (18.98)	0.55	1.24	0.30
Waitlist <i>n</i> =21	111.90 (28.01)	105.69 (24.43)	0.24	104.93 (22.46)	0.28		
Treatment–control difference			0.43		0.27		
Quality of life—CS psychological well-being							
Treatment <i>n</i> =19	5.25 (1.26)	5.63 (1.35)	−0.29	5.37 (1.22)	−0.10	0.516	0.60
Waitlist <i>n</i> =21	6.42 (1.45)	6.51 (1.20)	−0.07	6.40 (1.38)	−0.01		
Treatment–control difference			−0.22		−0.11		
Quality of life—CS spiritual well-being							
Treatment <i>n</i> =19	5.91 (2.02)	6.57 (1.79)	−0.35	6.14 (1.99)	−0.11	3.44	<0.05
Waitlist <i>n</i> =21	6.31 (2.10)	6.02 (1.94)	0.14	6.02 (1.81)	0.15		
Treatment–control difference			−0.49		−0.26		
Quality of life—CS physical well-being							
Treatment <i>n</i> =19	7.68 (1.95)	7.59 (1.82)	0.05	7.04 (1.79)	0.34	1.72	0.19
Waitlist <i>n</i> =21	7.79 (1.27)	8.01 (1.32)	−0.17	7.91 (1.10)	−0.10		
Treatment–control difference			−0.22		0.44		
Quality of life—CS social well-being							
Treatment <i>n</i> =19	6.26 (2.05)	6.48 (1.91)	−0.15	6.75 (1.78)	−0.26	0.618	0.54
Waitlist <i>n</i> =21	7.31 (1.21)	7.54 (1.18)	−0.27	7.47 (1.59)	−0.19		
Treatment–control difference			0.12		−0.07		
Neuropsychological outcomes							
CVLT-II-Total (<i>T</i> -score)							
Treatment <i>n</i> =19	60.00 (11.17)	63.63 (9.07)	−0.36	68.47 (9.71)	−0.81	3.161	<0.05
Waitlist <i>n</i> =21	62.10 (12.12)	60.62 (8.76)	0.14	64.21 (11.52)	−0.18		
Treatment–control difference			−0.50		−0.63		
Digit symbol–coding							
Treatment <i>n</i> =19	12.53 (3.31)	14.05 (2.95)	−0.46	14.42 (2.98)	−0.60	0.9	0.41
Waitlist <i>n</i> =21	12.00 (2.63)	13.07 (2.16)	−0.45	13.33 (2.95)	−0.48		
Treatment–control difference			−0.01		−0.12		
Color word trial ^a							
Treatment <i>n</i> =19	55.76 (15.30)	50.18 (10.51)	0.43	49.53 (9.65)	0.50	1.56	0.22
Waitlist <i>n</i> =21	55.50 (12.13)	51.41 (8.78)	0.39	50.26 (8.67)	0.50		
Treatment–control difference			0.04		0.00		
Color word ^a switching trial							
Treatment <i>n</i> =19	58.82 (9.55)	57.18 (11.12)	0.16	56.63 (8.08)	0.25	1.28	0.29

	Baseline Mean (SD)	Post-Tx Mean (SD)	<i>D</i>	2-Month f/u Mean (SD)	<i>d</i>	<i>F</i>	<i>p</i>
Waitlist <i>n</i> =21	58.10 (12.43)	56.14 (11.68)	0.16	56.10 (14.9)	0.15		
Treatment–control difference			00		0.10		
Trail making number–letter trial ^a							
Treatment <i>n</i> =9	63.99 (20.41)	60.68 (23.45)	0.15	54.53 (19.34)	0.48	0.23	0.80
Waitlist <i>n</i> =21	62.05 (19.36)	59.07 (17.03)	0.16	51.31 (16.22)	0.60		
Treatment–control difference			–0.01		–0.12		

Note: *d*=Cohen's *d*. Each *d* in the table is the within group size of effect reflecting change from baseline at post-treatment, and 2-month follow-up, respectively. The treatment–control difference in effect size is the control group effect size subtracted from the treatment group effect size. Negative or positive signs in front of effect sizes do not affect magnitude of effect (larger integer=greater effect).

^aLower MASQ scores indicate fewer cognitive problems and lower scores for both Color-Word Interference and Trail Making Tests indicate better performance. By contrast, higher QOL-CS scores, CVLT-II, and Digit Symbol-Coding scores indicate clinical improvement.