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Cognitive behavioral therapy for cancer related cognitive dysfunction

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Abstract

Purpose of review—To provide the reader with an overview of the cognitive-behavioral conceptualization of cancer related cognitive dysfunction (CRCD) and how cognitive behavioral therapy (CBT) can play an important role in treatment.

Recent findings—Recent findings show that Memory and Attention Adaptation training (MAAT), a CBT developed to help cancer survivors develop adaptive skills to improve daily cognitive performance and emotional coping, may be an efficacious treatment of CRCD and can be delivered through videoconference technology to improve survivor access to care.

Summary—The etiology of CRCD remains largely undetermined and likely is produced by multiple mechanisms. This can include neuronal death, microvascular damage, inflammatory processes and psychological factors of perceptions of inadequate cognitive capacity to meet performance demands and related emotional distress. As a result, there are a variety of treatments currently being researched. More research with larger sample sizes, multiple clinicians and multiple sites are needed to confirm efficacy, but CBT approaches such as MAAT that address multiple psychological factors involved may offer a flexible non-pharmacological approach to CRCD that optimizes quality of life outcomes.

Keywords

Cognitive behavioral therapy; cancer; cognitive dysfunction

Introduction

Cancer survival rates over the last 50 years have improved significantly, largely due to early detection of disease and more effective treatment (1). The present 5-year relative survival rate of all cancers is 68%, while worldwide, there are 32.6 million cancer survivors (2). In the midst of this good news is the public health concern of growing numbers of survivors

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with late effects of disease, treatment or both. Addressing the unique needs of cancer survivors to optimize long-term health function and quality of life well beyond the cessation of active cancer treatment is a priority in cancer care (1, 3).

Late cognitive effects of systemic therapies for non-central nervous system (non-CNS) disease is an ongoing focus of survivorship research and health care (4–6). Reviews of research over the last 2.5 decades estimate rates of long-term cancer-related cognitive dysfunction (CRCD; 1 year post-treatment) range from about 25% to nearly 50% (4–6).

Neuropsychological domains most commonly affected involve verbal memory, verbal working memory, attention and processing speed (4, 7). In most cases, the level of cognitive impairment when assessed by standardized neuropsychological tests is within a mild or moderate range and often at the lower end of neuropsychological testing norms (6). Higher quality studies of both cross-sectional and longitudinal designs have controlled for confounding factors that contribute to cognitive dysfunction such as depression, fatigue, anxiety and past history of CNS injury, suggesting that systemic therapy (e.g., chemotherapy and/or endocrine therapy) does cause cognitive decline among some individuals (4–6).

While CRCD is objectively assessed as mild to moderate with neuropsychological measurements, the quality of life impact can be substantial (8, 9). When survivors begin to resume pre-cancer vocational or social roles following active treatment, cognitive performance demands increase. It is often at this time point in survivorship when decrements in cognitive function begin to interfere with daily vocational, educational or family function (8–11). Intervening at this stage of survivorship (or ideally, before) is the intention of Memory and Attention Adaptation Training (MAAT) and other CBT approaches.

Cognitive-Behavioral Conceptualization of CRCD

The etiology of CRCD is thought to involve multiple mechanisms, including neuronal death through direct toxicity, microvascular damage, and neural disruption through inflammatory processes (12). A cognitive-behavioral conceptualization is concerned less with the biological event(s) triggering CRCD but more with the individual's psychological response to injury. MAAT assumes a "diathesis-stress" conceptualization. Under routine and low demand conditions, interacting neurocognitive systems (memory, attention, planned behavior and emotion regulation) function well for survivors. By contrast, under conditions of increased demand, cognitive failures may be more frequent and produce negative consequences. It is at this point where the survivor experiences a perception of disparity between "perceived threat level" (or increased demands on memory) and available resources (lowered perceived cognitive abilities) that leads to increased arousal, distress and in turn reduced cognitive performance. The perception of disparity of memory demand and perceived cognitive abilities is consistent with the Lazarus (13) two-step appraisal model of stress. That is, perceptions of threat or increased demands for memory performance are not enough to trigger stress responses— it also requires the perception that personal or external resources are inadequate to meet the threat. This process is depicted on the right side of Figure 1. Perceptions of inadequate cognitive abilities can increase emotional arousal, leading to cognitive interference with attention, encoding and recall, leading to an attribution of distress-related cognitive interference to CRCD-reinforcing confirmatory beliefs of

inadequate cognitive abilities. These psychological responses are hypothesized to not "cause" CRCD but play a maintaining role in the distressing experience. The "diatheses" of CRCD include vulnerabilities in cognitive function produced by the survivor's exposure to chemotherapy and other factors such as pre-cancer neurocognitive status, education, age, genetic predispositions, cognitive reserve (5) and emotional resilience (3). The more survivors with CRCD can train and make effective use of existing cognitive capacities AND learn and apply new skills, the better the cognitive task performance, perceptions of memory self-efficacy (the belief one has the skills or resources to meet demands) and distress reduction. MAAT's central aim as a CBT is to build adaptive skills and mastery experience to reduce disparity between perceived coping resources and cognitive demands.

There is evidence supporting this model from brain imaging literature. Compared with healthy controls and breast cancer survivors not undergoing chemotherapy, survivors who have had chemotherapy appear to have nearly similar objective memory test performance. Yet, chemotherapy-exposed survivors demonstrate significantly more cortical activation and report more subjective symptoms during task performance, especially with increased task difficulty (14–16). This may explain why survivors report more subjective complaints than healthy counterparts but may score in normal neuropsychological test ranges and encounter greater cognitive failure at the point of resuming pre-cancer work and home roles (6).

CBT and MAAT

In the treatment of CRCD, CBT differs from traditional cognitive retraining. Cognitive retraining involves repetitive tasks to hypothetically enhance neural networking to bypass damaged brain regions. This usually entails computerized exercises with incremental increases in task difficulty based on performance (e.g., once 85% correct response is achieved, the practice task increases in difficulty, and the process is repeated). The "dosing" of daily practice varies but one study suggests daily sessions of 20–30 minutes for 12–15 weeks (17). By contrast, CBT involves the acquisition of skills to make adaptive behavioral and cognitive changes on daily tasks for which memory is used (18, 19). For example, this might include using a verbal rehearsal method to aid working memory for transposing numbers from a computer to a written form at the workplace, or learning how to use and apply a smart phone calendar with alerts to transition to important tasks such as paying a household bill.

In recent reviews, cognitive retraining was found to be helpful but one shortcoming of the approach is the lack of generalizability or "transfer" of cognitive improvement from practice tasks (computer game) to real-world tasks (2, 20–22). CBT enhances self-awareness of where memory problems are likely to occur and directly trains individuals to apply compensatory strategies in those specific cognitive tasks. This might involve self-monitoring of memory failures to better understand the environmental and internal personal factors that contribute to the memory failure risk of a given individual so that compensatory strategies designed to reduce memory failure occurrence can be learned and targeted for specific situations. Two CBT approaches cited in some of these reviews were delivered in 5 or 4 weekly group visits. Both were found to improve neurocognitive outcomes in domains of verbal memory and processing speed and self-reported cognitive symptoms (23, 24).

However, the Ercoli study did not involve any control group which limits conclusions due to the effects of practice with repeat neurocognitive testing (23). Similarly, the Schuurs study had limitations. While the investigators used a wait-list control group to account for neurocognitive testing practice effects, participants were not randomized to either the treatment or control condition. This brings into question the possibility of selection bias in the final sample— for instance, participants in the treatment condition (N = 23) could have put forth greater effort in neurocognitive testing and report more favorable self-reports of cognitive function post-treatment. In addition, some of the neurocognitive assessments were conducted by one of the interventionists in the study, which the authors report as a limitation (24).

At present, the MAAT CBT approach has evidence in three small studies (N = 29, 40 and 35, respectively) with improved methodology (e.g., blind assessors, randomization) that demonstrate gains in neurocognitive outcomes, self-reported cognitive symptoms and quality of life (10, 25, 26). This research is highlighted below with a more detailed description of MAAT.

As a CBT, MAAT's current format involves eight weekly visits of 30-45 minutes duration and can be delivered effectively through videoconference technology (10). Survivors are provided a workbook to reinforce learning and mastery of skills covered in visits. MAAT has four components: 1) Education on chemotherapy-related cognitive problems and other influences on normal attention and memory such as stress "normal forgetting" (27-29). This reduces misattribution that **All** daily memory failure can be due to chemotherapy—a less controllable causal attribution- and raises the possibility of more controllable causes such as stress response. This causal attributional shift may enhance coping with CRCD through stopping the iterative distress cycle seen in Figure 1. 2) A second key aspect of MAAT is self-awareness training. That is, using self-monitoring to help survivors identify "at risk" environmental, social, physical or emotional conditions under which cognitive failures occur, which enables survivors to tailor compensatory strategies to specific tasks. 3) Compensatory strategies training for application in "at risk" situations that may directly improve cognitive performance. Common compensatory strategies include Self-Instructional Training (SIT), or a method of "self-talk" to enhance on-task attention, using a day planner, verbal rehearsal, active listening and visualization strategies. 4) Stress management methods of applied relaxation training, cognitive restructuring to modify negative appraisals of cognitive failure with activity scheduling for arousal and stress self-regulation (30–32).

MAAT Research: Study 1—MAAT was pilot tested for feasibility and to determine if it could positively influence daily cognitive symptoms, neurocognitive test performance and quality of life. In a single-arm pilot study (25), 29 breast cancer survivors (mean 8.2 years post-chemotherapy) reporting cognitive problems completed MAAT. Principal outcome measures included the Multiple Ability Self-Report Questionnaire (MASQ; self-report of cognitive function in daily life)(33), the Quality of Life-Cancer Survivors scale (QOL-CS) (34), satisfaction ratings and a brief neurocognitive test battery administered at baseline, post-treatment, two-month and six-month follow-up with supplemental funding. Results indicated significant reductions in daily cognitive complaints, improved quality of life and high satisfaction. Neurocognitive improvements in verbal memory and processing speed

MAAT Research: Study 2—The second MAAT study was a small waitlist (no treatment) control RCT (31). Forty breast cancer survivors at least 18 months post-chemotherapy and reporting cognitive problems were randomized to MAAT (n = 19) or waitlist control (n = 21) conditions and assessed at baseline, post-treatment and two-month follow-up. Controlling for education and IQ, MAAT participants made significant improvements over waitlist participants on quality of life and verbal memory as assessed by the California Verbal Learning Test-II (CVLT-II). Subtracting wait-list control effects, the pre-to-post-treatment effect size for the CVLT-2 total score was -.50 and quality of life effect size was -.49 (note that the negative sign does not change the magnitude of effect). CVLT-II scores for MAAT participants also improved at two-month follow-up (d = -.63). While results in this small RCT were encouraging, an active control condition was needed to rule out effects of social attention and demand characteristics of study participation. In addition, improvement in selfreport and neurocognitive outcome measures had been improved upon and were incorporated in the next trial. MAAT was also intended to be electronically delivered with videoconference technology to improve access to survivorship care, which has been a challenge for both comprehensive and community cancer centers (1, 35).

MAAT Research: Study 3—In the third MAAT trial, Ferguson, et al. (2016) added an active control condition, supportive therapy (ST) and increased the number of weekly MAAT visits to eight to enhance therapeutic intensity (10). ST is a common active control condition in CBT trials to control for psychological therapy "common factors" such as interpersonal warmth, empathy and treatment expectation. The Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog) was added as a primary self-report outcome measure which was available at the time of design of the third MAAT trial (36). Both MAAT and ST were delivered via videoconference network linking rural health centers in the state of Maine. The primary aim of the study was to evaluate electronic delivery feasibility/ efficacy with a small final sample size (N=35). Adjusting for baseline differences, MAAT participants improved in FACT-Cog perceived cognitive impairments over ST at two-month follow-up with moderately large effect size (p = .02; d = .52; trend at post-treatment p = .09). In neurocognitive outcomes, MAAT participants made significant improvement in processing speed over controls at post-treatment (p = .03; d = .50) but not on verbal memory. Finally, MAAT participants had a trend (p = .07) of improvement over ST in anxiety about cognitive symptoms (meta-memory in adulthood anxiety scale) but with a large size of effect (d = .90) at two-month follow-up. This suggests MAAT participants continued to make gains in emotion distress reduction through continued mastery and use of coping skills while ST participants (who did not receive skills training) regressed to baseline two-months after cessation of therapeutic attention. MAAT participants reported high satisfaction with treatment and they were highly likely to recommend treatment to a friend. Finally, MAAT participants indicated they likely would have not been able to participate without videoconference delivery due to travel burdens and lack of paid leave from work that was exhausted during active cancer treatment.

Conclusion

At the present time, there are several treatment approaches to CRCD that range from pharmacological approaches, physical activity and computerized cognitive retraining (20–22) but no treatment is empirically established as a standard for clinical use. CBT does offer a practical approach for enhancing cognitive function and quality of life improvement in daily life to address the consequences of CRCD in long-term survivorship. MAAT is one CBT approach that has accumulated preliminary evidence of efficacy and can likely be easily translated to survivorship service given that CBT is reimbursed by third party payers when delivered by trained professionals (e.g., psychologists, psychiatrists, psychiatric nurse practitioners and licensed counselors). Moreover, recent research suggests MAAT can be flexibly delivered using videoconference technology with positive outcomes.

While promising, MAAT research to date has limitations that should be addressed in future investigations. These limitations apply to the other CRCD treatment approaches cited here and include: small sample sizes, only one clinician delivering active treatment or the active control condition (e.g., MAAT and ST/attention control), single research sites and most research has been limited to breast cancer survivors only (8, 20–22). Recent reviews of CRCD treatment research have recommended that future trials utilize multiple sites with multiple clinicians and active treatment control conditions. With these methodological improvements, there will likely be an increase in confidence of results with respect to external validity and generalizability of treatment that can readily translate to clinical practice for survivors. Much of the research funding for CRCD has focused primarily on identifying specific mechanisms of cognitive change in various cancer populations with less funding targeting CRCD treatment research. Larger funding mechanisms, collaborations between institutions with multi-site trials and combining treatment research with imaging research may be one solution to address resource limitations for CRCD treatment and also help identify questions of how treatment can enhance CRCD recovery.

Finally, utilization of various forms of treatment delivery, including videoconference technology, may reduce barriers to survivorship care access and increase dissemination of CBT for CRCD. MAAT does have some evidence of effective videoconference delivery and larger, multisite studies such as those described above are planned. MAAT may also be delivered in group formats to leverage time and space in busy clinical settings. In addition, self-guided mobile device apps of interventions of CRCD may provide even further survivor access to care and may be more convenient and affordable than standard CBT (37). However, some research suggests that web-based or mobile-device self-guided apps are viewed as less than satisfactory for a majority of research participants in studies of such treatments(38). Nonetheless, they do appear to be helpful for some. In future research on CBT for CRCD, it may likely be most fruitful to develop a range of less intensive to more intensive therapeutic approaches in a stepped care fashion that allows more survivor choice and tailoring to individual needs.

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Key points

- Cancer related cognitive dysfunction affects many cancer survivors todaybecause its etiology is not known, there have been a wide array of treatment trials.
- Cognitive behavioral therapy is one treatment modality that has been evaluated and can be tailored to the specific areas of concerns that cancer survivors have.
- A specific type of CBT, MAAT, has been shown in several studies to help improve patient's quality of life and improved neuropsychological test outcomes but more research with multiple clinicians and multiple sites is needed to confirm effica

Diathesis-Stress and Appraisal Model of CRCD and MAAT Components of Change

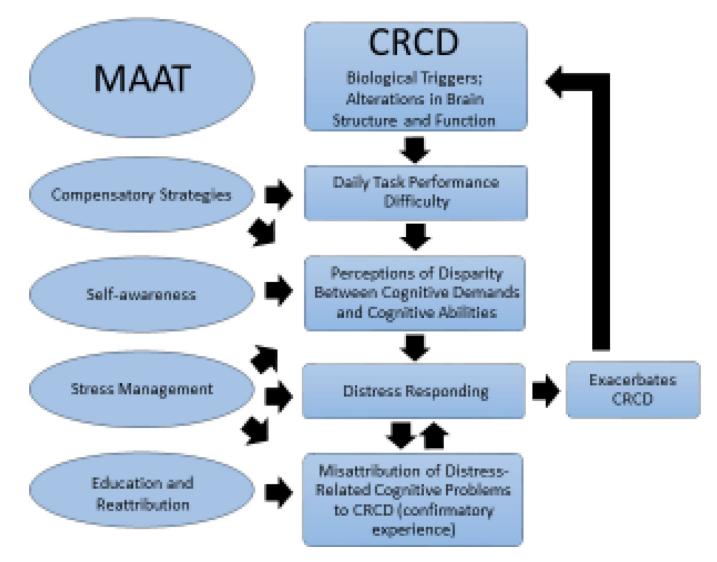


Figure 1. Diathesis-Stress and Appraisal Model of CRCD and MAAT Components of Change.