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Neuropsychological Care and Rehabilitation of Cancer Patients With Chemobrain: Strategies For Evaluation and Intervention Development

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Abstract

Malignant tumors and their various treatments such as chemotherapy, radiotherapy and hormonal therapy can deleteriously affect a large number of cancer patients and survivors on multiple dimensions of psychosocial and neurocognitive functioning. Oncology researchers and clinicians are increasingly cognizant of the negative effects of cancer and its treatments on the brain and its mental processes and cognitive outcomes. Nevertheless, effective interventions to treat cancer and treatment-related neurocognitive dysfunction (CRND), also known as chemobrain, are still lacking. The paucity of data on effective treatments for CRND is due, at least partly, to difficulties understanding its etiology, and a lack of reliable methods for assessing its presence and severity. This paper provides an overview of the incidence, etiology, and magnitude of CRND, and discusses the plausible contributions of psychological, motor function, and linguistic and behavioral complications to CRND. Strategies for reliable neuropsychological screening and assessment, and development and testing of effective ways to mitigate CRND are also discussed.

Keywords

Cancer and Treatment-related Neurocognitive Dysfunction; Chemobrain; Cancer and Memory Problems; Cognitive functioning; Neuropsychological Tests; Chemotherapy; Cancer and Cognition; Cognitive Disorders; Neoplasms; Malignant Tumors; Mental Performance

INTRODUCTION

Impact of cancer and its treatments on neurocognitive functioning

Malignant tumors and their various treatments (e.g., chemotherapy, radiotherapy, hormonal therapy, biologic therapy, or combined treatment modalities) can adversely impact the brain

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and disrupt its neuronal activities and their associated cognitive functions. Cancer and treatment-related neurotoxicities have been linked to deficits in cognitive systems that support attention, memory, processing speed and executive function [1-5]. Impairments in key domains of attention (e.g., focused and sustained attention, selective attention, and distractibility), memory (e.g., immediate and delayed memory, short-term or working memory, and verbal and visual memory), processing speed (e.g., cognitive data manipulation), and executive function (e.g., planning, organizing, problem solving, abstract thinking, mental flexibility, cognitive insight or the ability to monitor and correct one's own conviction) can deleteriously affect patients and survivors on multiple psychosocial, economics, emotional, interpersonal, relational and quality of life dimensions.

Incidence and magnitude of cancer and treatment-related neurocognitive dysfunction

Cancer and treatment-related neurocognitive dysfunction (CRND), also known as chemobrain or chemo fog, has been reported in up to 75% of patients and survivors with non-central nervous system malignant tumors (e.g., breast, head and neck, cervical, prostate and colorectal cancers) [6-8]. CRND is a lasting and debilitating adverse condition [9-10]. An epidemiologic study using data from a large national, stratified, multi-stage probability sample of civilian, non-institutionalized population in the United States reported a greater likelihood of self-reported memory problems among individuals with a history of cancer than those without any history of cancer. Specifically, this study reported that adjusting for common predictors of memory impairments such as older age, sex, race-ethnicity, educational achievement, poverty level, and poor general health, individuals with a history of cancer were forty percent more likely to report having memory problems that interfere with their activities of daily functioning [11]. CRND is of particular significance to cancer symptom management research because of its prevalence and adverse effects on psychosocial functioning and overall quality of life of patients and survivors.

Etiology and proposed theories of CRND

Albeit not yet clearly understood, researchers have proposed a number of possible causes for CRND that stem both from the cancer itself as well as its treatments (Figure 1). Some of the possible factors implicated in CRND include altered brain biochemistry, genetic predisposition to cognitive declines, tumor metastases to the brain, failure of the blood-brain barrier, deoxyribonucleic acid damage, telomere shortening, defects in neural repair, demyelination, microvasculature obstruction, infarction of brain tissues, oxidative stress, changes in hormonal levels, and abnormal cytokine activities [12-17]. These aforementioned factors may be independently or synergistically implicated in CRND, and may differentially exacerbate cognitive problems based on patients' personal characteristics such as age, education, cognitive reserve, and psychological and behavioral comorbidities [18-19].

This paper presents a framework for the neuropsychological care and rehabilitation of cancer patients and survivors. Possible contributions of psychological, motor, language and behavioral variables to cognitive impairments are discussed. We also discussed essential steps in the assessment (e.g., determining the goals and benefits of the neurocognitive evaluation, preparing patients for cognitive testing, and selecting appropriate tests) and management of CRND.

Psychological, Motor, Language, and Behavioral Contributions to CRND—

Psychology plays an essential part in the cancer care process, including helping patients identify and manage psychological distress related to cancer diagnosis and symptomatology, coping and adjusting to their condition, adhering to recommended treatment regimens and follow-up, cancer, and dealing with plausible survivorship difficulties. Researchers and clinicians are becoming increasingly cognizant of the impact of cancer and treatment-related adverse effects, especially neurocognitive impairments, on survivorship and quality of life. Understanding psychological and behavioral factors that may be implicated in CRND is essential to its characterization and the development and testing of reliable interventions to treat this debilitating condition.

Psychological contributions to CRND

Psychological distress such as depression and anxiety can impact mental processes and cognitive performance both directly and indirectly, and may be implicated as a causative factor in CRND [20-22]. The direct effect of anxiety and depression on cognitive functioning has been extensively studied and is particularly problematic for networked functions such as attention and memory [23-25]. Growing evidence suggests that psychological states may also have an indirect effect on cognitive functioning. For example, previous studies have reported significant associations between depression and changes in brain structures (e.g., ablation of hippocampal neurogenesis), functional neuroanatomical or structural processes (e.g., hippocampal activation), and cognitive operations, which are critical to cognition and behavioral outcomes such as attention and memory [26-28]. In addition, cancer and treatment-related neurotoxicities can aggravate premorbid psychological distress and neurocognitive impairments.

Interests in the involvement of immune system responses in psychological distress, specifically the relationship between inflammatory cytokines and mood states (e.g., depression and anxiety) are steadily growing [29]. Depression and anxiety have been linked to acute inflammatory immune responses based on elevated blood levels of C-reactive protein and higher concentration of inflammatory cytokines such as interleukin- (IL)-6, IL-1beta, tumor necrosis factor alpha (TNF- α), and IL-1 receptor antagonist [29-30]. The underlying neurobiological mechanisms linking psychological distress and CRND are not yet clearly described. Nonetheless, cancer and its various treatments have been associated with inflammatory immune responses that may negatively influence the relationship between psychological distress and cognition [31-33]. Previous studies also support the hypothesis that inflammatory immune responses and neuronal changes within the hippocampal formation (e.g., the dentate gyrus, plays a functional and modulating role in stress and psychological distress through the release of glucocorticoids) could impact the relationship between psychological distress and memory impairment [34-39].

Contributions of motor and language complications to CRND

While not yet systematically examined, pre-existing and acute cancer and cancer treatment-related motor and language complications may also be involved in CRND. Most cognitive measures require intact language capacity to comprehend task instructions and to verbalize responses, or require intact motoric capacity to provide written responses. Studies examining

cognitive issues related to cancer and cancer treatment-based language complications are lacking. In fact, studies on language impairments in the context of cancer and its treatments generally focused on limited cancer populations such as head and neck (HNC) and central nervous system (CNS) cancers [39-41]. Systematic examinations of the contributions of motor and language problems to neurocognitive dysfunction among non-HNC and non-CNS cancer patients and survivors are needed.

Behavioral and functional implications

CRND can adversely impact behavioral and functional operations that are central to one's ability to successfully participate in normal activities of daily functioning. Diminished abilities in psychological and neurobiological drives (e.g., adynamia and motivation) and intrapersonal processes and self-control (e.g., impulsiveness, disinhibition, verbosity, tangentiality, irritability, fidgety, and low frustration tolerance) may have significant interpersonal and relational implications for cancer patients and survivors.

Adynamia (i.e., lack of strength and/or vigor due to pathological conditions) and motivation (i.e., the desire to get involved and complete certain activities) are not yet systematically examined in cancer control or symptom management research. However, a growing number of cancer control studies have examined the relationships among cancer, chemical and radiologic therapies, and fatigue [42-46]. Lack of strength and/or vigor associated with cancer and cancer treatments has been examined through research on cancer-related fatigue (CRF). CRND could also be linked with CRF. Surprisingly, studies on the association between CRF and CRND are still lacking.

Studies on CRF have provided indirect opportunities to assess and evaluate adynamia. Future prospective studies are needed to more systematically examine the presence, severity, and possible debilitating effects of adynamia in cancer patients and survivors. Systematic studies of adynamia in cancer populations could enhance our understanding of CRND and guide the development of intervention to treat this debilitating condition to the extent that adynamia and CRND have a common or overlapped pathway. Similar to the lack of studies on adynamia, there is a paucity of data on the impact of cancer and treatment-related difficulties in intrapersonal processes and self-control (e.g., impulsiveness, disinhibition, verbosity, tangential, and irritability, and low frustration tolerance). Well-thought-out and carefully implemented neuropsychological procedures could provide valuable insights on intrapersonal processes and self-control issues. Reliable and valid neuropsychological data are needed to guide the development and testing of effective interventions to treat CRND.

Neuropsychological Assessment of Cancer-Related Neurocognitive Dysfunction

Goals and Benefits of Neuropsychological Evaluation: Understanding the neurobiological and psychological mechanisms of cancer and treatment-related impairments in cognitive processes and behavioral outcomes (e.g., loss of higher reasoning, forgetfulness, and problems in attention and memory) is essential to the characterization of CRND and the development of effective interventions to treat this debilitating side effect. Psychologists play a variety of roles in the evaluation and treatment of CRND. Neuropsychological

assessment can be performed to help determine the presence and severity of CRND, monitor its clinical course, and evaluate the effectiveness of interventions to treat this condition for patients and survivors. Assessment of neuropsychological functions typically provides information to facilitate recommendations for rehabilitative efforts, highlighting potential obstacles to rehabilitation and long-term recovery, and outlining functional impairments that can be reasonably inferred from neuropsychological tests data (e.g., inability to carry out routine activities of daily functioning). Neuropsychological assessment is also useful in determining issues related to decreased cognitive abilities or lack of awareness of impairments, and for addressing motivational and emotional issues that could diminish quality of life for patients.

Preparing Cancer Patients for Testing—Patients undergoing neuropsychological evaluations should be informed about the nature and purpose of testing so that any fears or concerns can be addressed. While most patients are familiar with the activities that transpire during a medical appointment, few will know about the activities or purpose of a neuropsychological assessment. Inasmuch as cognitive functioning is integral to one's sense of competency, some patients may become defensive about the validity of the neuropsychological evaluation or even refuse to participate altogether. Allaying these types of concerns at the outset is an important first step in establishing rapport and setting the stage for a cooperative evaluation process.

Accurate and valid neuropsychological evaluation is predicated on certain prerequisites that permit professionals to attribute impaired performance to CRND and not to extraneous factors. Patients must be able to sustain sufficient arousal to attempt completion of cognitive tasks, which is frequently a challenge during the acute stages of illness or immediately following some treatments. Additionally, patients must have adequate integrity of sensory functions to utilize test stimulus materials. For tests that require manipulation of test materials or writing, patients must have adequate function of the upper extremities. Lastly, patients must have adequate attention to be able to attend to test instructions and changing contingencies and tasks demands. The presence of one or more of these problems could cause a decreased in performance on neuropsychological tests that may be unrelated to the patient's cognitive state.

Use of Contextual information—Accurate interpretation of standardized test results requires contextual information that begins with a careful review of the patient's case history and medical records, and interviews with the patient and his/her family members. The clinical interview is particularly important in the identification of relevant information about history and subtle changes in behavior and cognition observed by patients and their family. However, patients can also distort factual information, which is why it is important to verify self-reported information whenever possible. For example, a patient's self-report about school performance can be greatly exaggerated. While accurate data is important in all major life domains it is of particular significance in the areas of educational attainment, previous neurological risk factors such as history of neurological illness or injury, and premorbid or current substance abuse. The unifying theme of the clinical interview and history is to seek consistency in available information. Specifically, uniformity of

information in terms of patients presenting complaints, performance on cognitive tests, observations from family members, injury characteristics as identified in medical records, impairment in activities of daily living, and consistency in symptomatology presentation over time.

General Considerations for Test Selection—Decision about the content of a neuropsychological battery of tests is important and should be based on testing objectives and more specifically what broad and/or specific areas of cognitive functioning need to be examined. Currently, there are hundreds of tests available with which one could conduct a neuropsychological evaluation. However, few of these tests have acceptable reliability and validity, especially ecological validity for cancer populations. A comprehensive neuropsychological evaluation should focus on determining the integrity of all major cognitive domains (e.g., sensory and perceptual, verbal and nonverbal intelligence, simple and complex attention, processing speed, learning and memory, language, motor; and executive functions). Comprehensive neuropsychological evaluation takes considerable time to complete (e.g., eight or more hours of direct face-to-face testing time plus additional time for test scoring, interpretation, and report preparation). When patient fatigue threatens to compromise the validity of test results, it is common to break the assessment period into several smaller assessments across multiple days. Nevertheless, an evaluation of this length is generally impractical in oncology settings for many reasons including clinical time constraints and patient fatigue. Additionally, a comprehensive neuropsychological testing for CRND may not be reimbursed by insurance payors. Nevertheless, a good neuropsychological evaluation should attempt to strike a balance between being comprehensive and adequately sampling areas commonly impaired in CRND.

Consensus development studies examining the most reliable and valid approaches to assess the presence and severity of CRND are still lacking. However, despite the lack of “gold standard” measures standardized for cancer populations, CRND studies generally use readily available objective and psychometrically validated neuropsychological tests. Therefore, the presence of CRND is normally based on the comparison of neuropsychological test data from cancer patients with data from people without any history of cancer or cancer treatment [46]. Irrespective of issues related to the ecological validity of currently available neuropsychological tests for cancer populations, these currently available neuropsychological measures can provide valuable data to patients, psychologists, and rehabilitation specialists if selected, administered, and interpreted competently within the context of patients’ personal and clinical characteristics, medical history, psychosocial conditions, family history, and premorbid level of neurocognitive performance.

Fixed versus Flexible Test Batteries—Whether one uses a flexible or a fixed type battery of tests is of importance. In a flexible battery a group of individual tests are selected for each cognitive domain, each with established validity for detecting brain impairment. In a fixed battery approach (e.g., Repeatable Battery for the Assessment of Neuropsychological Status; Halstead-Reitan Neuropsychological Test Battery), tests are used which have collectively as a group been shown to be sensitive to brain impairment. There are several advantages and disadvantages of one approach over the other (i.e., flexible versus fixed

neuropsychological assessment batteries). Flexible batteries, as the name implies, have the capacity for being adapted to the needs of a specific patient. Fixed batteries provide relatively broad examination across most cognitive domains. However, the tests of fixed batteries may rely on multiple cognitive domains; thus complicating interpretation of outcome data. Additionally, there is inadequate normative data for some tests and summary scores, and some domains like intelligence and memory have either cursory assessment or are not assessed at all. Fixed batteries also have the distinct advantage of providing the same basic tests across patients, which greatly facilitates research endeavors. Because of these aforementioned reasons, many neuropsychologists use a hybrid approach in which a “fixed-battery” is supplemented with additional “flexible-battery” tests.

Mapping Cognitive Changes Over Time—Also of importance is whether tests have alternative forms (i.e., highly similar but not identical test) available so that repeat measurements can be conducted without concern for potential practice effects artificially elevating test performance. If alternative forms of a test are available, then it is possible to complete retesting of the same cognitive domains over time. There are two alternative approaches that can be applied when alternate test forms are unavailable. One can either wait a sufficient interval of time (e.g., between 6 to 12 months depending of the cognitive domain of interest) between testing and retesting to minimize or eliminate practice effects. Another approach is to statistically account for possible practice effect. There are now correction factors that have been established that allow for a “reliable change index” after accounting for expected practice effects.

Acceptable Test Adaptations for CRND—While nearly all psychometrically validated tests of cognitive abilities have procedures for standardized administration, there are variations in standard practice throughout clinical practices. Variation of standardized procedures may be for appropriate rationale, such a desire to “test the limits” of the individual’s abilities by modifying procedures, as well as inappropriate reasons such as improper administration, convenience, or personal preference. It is also sometimes necessary to adopt special strategies for gaining maximal test performance when working with persons with impairments such as patients with CRND. Although not specifically addressed in most test manuals, clinicians might need to work harder at developing appropriate patient-provider rapport to facilitate testing. For example, clinical psychologists/neuropsychologists might need to provide encouragement for patients to remain task-oriented, assist with managing frustration due to poor test performance, provide frequent repetition of test stimuli and instructions, or choose alternate measures to accommodate physical limitations. When the purpose of the evaluation is to obtain the individual’s best performance, it can be appropriate to modify standardized test procedures for persons with disabilities while still preserving important aspects of the standardized administration [47-48].

Modification of test procedures is most commonly done when a patient has physical or sensory limitations. Careful test selection should be the first choice when confronted with these limitations, and can obviate the need for any test modification. For instance, in patients with upper limb motor problems it may be wise to select tests that do not require manipulation of objects or writing [49]. For persons with visual impairment it might be

possible to use tests with auditory stimuli, or to use visually mediated tests for those with impaired hearing. A second tier choice is actual modification of test procedures and stimuli. Rephrasing questions or elaborating on instructions, if done carefully and competently, can allow the patient to complete the tests while still preserving test validity. Stimuli for some tests can be enlarged for those who have visual impairments. Psychologists might need to enlarge the materials themselves, although for some tests, enlarged print or stimuli can be purchased. For those with unilateral visual field inattention, stimuli can be placed in the intact visual field instead of the patient's midline. For some verbally-mediated tests, recognition items have been developed for those who have expressive communication deficits [50].

A number of modifications of various tests have been reported in the literature for other specific populations, though no literature exists for patients with cancer. When done cautiously, adaptations offer the possibility of making neuropsychological tests more appropriate and meaningful for the population being assessed, which may increase our ability to draw valid inferences [51].

Cognitive Tests for CRND—Cancer control studies of brain dysfunction and behavior generally focused on few aspects of cognitive functioning such as attention, concentration and memory. Nonetheless, various other aspects of cognitive functioning (e.g., processing speed, executive function, and perceptual and motor functioning) are also susceptible to the negative effects of cancer and cancer treatments. Previous reviews have addressed cognitive impairments related to CRND [52-53].

Despite discrepancies between patient self-reported complaints of cognitive impairments and scores on objective psychometrically validated neuropsychological tests, these objective measures of cognitive function can be useful in characterizing CRND. Additionally, currently available structured interviews and rating forms such as the Short Portable Mental Status Questionnaire, the Neuropsychological Impairment Scale, and the Patient Assessment of Own Functioning may also be useful in screening and evaluation of CRND. The neuropsychological examination should include tests of intelligence, personality, perception, motor function, attention and memory. The neuropsychological assessment is a dynamic process that generally varies as a function of (1) the specific purpose of the examination, (2) the general intactness of the individual examinee, and (3) the thoroughness of the examination: screening versus more comprehensive evaluation. Hence, a careful assessment of CRND should involve a multi-step approach ranging from screening of broad cognitive domains to a more comprehensive assessment of specific cognitive functions. This approach will prove helpful and more practical, especially in time constraint clinical oncology settings. When conducting a screening or comprehensive assessment of CRND, we need to be cognizant of the fact that cognitive functioning involves multiple complex processes in key domains and sub-domains of attention (e.g., focused, sustained, selective, alternating, and divided), memory (e.g., sensory, short-term, long-term), processing speed (e.g., reading, writing, math), and executive function (e.g., planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility, multi-tasking, and initiation and monitoring of actions). Examples of neuropsychological tests and their respective cognitive domains and sub-domains can be found in (Table 1).

Management of Neurocognitive and Behavioral Impairments in Patients with Cancer

Integrating Neuropsychological and Functional Evaluations—

Neuropsychological evaluation aims to assess brain and behavior relationships, whereas functional evaluations identify cognitive deficits in the context of performing everyday tasks and activities. Functional evaluations may include behaviors like scanning the environment for obstacles while ambulating, sequencing steps while dressing or preparing a meal, or remembering therapy activities performed during the day. The neuropsychological evaluation and the functional evaluation each contribute important, independent, information to the overall formulation of the patient's cognitive functioning. This formulation guides the treatment planning with regard to rehabilitation goals and cognitive interventions. Emphasis is increasingly being placed on the functional implications of cognitive assessment. Inferences about functional skills are now routinely based on cognitive test results.

Reasonably intact cognitive skills are arguably a prerequisite for most functional activities, although there tends to be more preserved performance on tasks that were previously learned and had been performed often compared to novel task performance following CRND. Despite the fact that the ecological validity of various tests is still debatable, clinical psychologists and neuropsychologists have made considerable strides in demonstrating the functional implications of cognitive deficits. Not infrequently, rehabilitation providers find that results of a neuropsychological evaluation can differ from results of a functional assessment. When this occurs, understanding the nature of the patient's cognitive presentation (and how to intervene) requires that we consider several factors. These factors include the circumstances under which the neuropsychological and functional evaluations occurred (e.g., environment, context, cues), novelty or familiarity with the cognitive tasks presented, amount of structure provided during the evaluations, and ecological soundness of the evaluation methods.

Developing and implementing a cognitive neuropsychological treatment plan

—While there has been a long tradition of applying cognitive remediation interventions to cases of acquired brain injury, such as traumatic brain injury, research examining cognitive remediation in patients with CRND has been extremely limited. Quality of life studies have almost exclusively focused on physical limitations to the exclusion of cancer-related cognitive concerns. The general efficacy of cognitive remediation has been extensively reviewed [54]. Based on a methodological review of the scientific literature, preliminary support for effectiveness of cognitive remediation interventions has been found in the areas of attention, memory, functional communication, and executive functioning.

The current status of CRND remediation is largely based on the adaptation and application of neurocognitive rehabilitation strategies from other clinical populations (e.g., mild cognitive impairment) to cancer patients and survivors. The types of rehabilitation interventions being adapted in cancer populations include direct cognitive remediation, compensatory training, and environmental change. Cognitive deficits and behavioral difficulties play a significant role in limiting effective adaptation and learning of ways to function successfully. Long-term disability generally results from the impact of cognitive and behavioral factors on functioning rather than primary physical impairment. Generally,

recovery follows a pattern of restoration of basic skills and abilities followed by recovery of more complex abilities. Subjective complaint of cognitive impairments in cancer patients and survivors usually occur in the absence of gross demonstrable pathology or neurological deficits. The most common cognitive complaints include memory and concentration, which are reported by up to 75% of cancer patients and survivors. At each stage along the cancer care continuum, the clinical psychologist or neuropsychologist may play several key roles: 1) conduct assessment and ongoing monitoring of neuropsychological functioning, 2) provide treatment recommendations and planning for cognitive, emotional, and behavioral impairments based on neuropsychological evaluation outcomes, 3) provide educational information to the treatment team, patient, and family regarding neuropsychological functioning, 4) implement interventions for behavioral management and emotional functioning, and 5) implement and monitor the effects of interventions to improve cognition.

The International Cognition and Cancer Task Force (ICCTF) (consisting of a multidisciplinary group of neuropsychologists, clinical and experimental psychologists, neuroscientists, imaging experts, physicians and patient advocates) and other cancer control researchers are working to help advance our understanding of the etiology and negative impact of CRND on quality of life and psychosocial functioning, and to identify strategies for reliable assessment and treatment of this debilitating condition. The ICCTF has also noted various issues ranging from heterogeneity of research methodologies and discrepancies between self-reported and outcomes of objectively measured cognitive impairments, which might have delayed progress in the development of effective treatments for CRND. To address these issues, the ICCTF is working on developing recommendations for a core set of neuropsychological tests, common criteria for defining cancer and treatment-related changes and impairments in cognitive function, and approaches to increase the homogeneity of study methods.

Dealing with psycho-behavioral correlates of CRND—Previous studies have indicated that psychological and behavioral interventions such as cognitive behavioral therapy, meditation, yoga, and physical activity or exercise can help mitigate CRND [55-58]. A review on the relationships among cancer, cognitive impairment, pharmacotherapy, meditation, and cognitive function reported that meditation might help alleviate cancer-related cognitive problems [55]. Another study examined the potential benefit of a brief cognitive behavioral treatment intervention (i.e., Memory and Attention Adaptation Training – MAAT) to treat cancer treatment-related cognitive problems for breast cancer patients on average eight years post chemotherapy. The findings revealed improvements in self-reported cognitive function after MAAT intervention, and at 2-month and 6-month follow-up. The findings also showed higher patient reported satisfaction and rating of the intervention [56]. Other studies have examined the effects of physical exercise on brain function and suggested that participation in physical exercise or activity may help increase blood flow and the supply of oxygen to the brain [57]. Exercise may also contribute to stimulation of brain structures involved in memory formation and help reduce brain-bound free radicals that can slowdown normal degradation of neurons and increase the production of brain-derived neurotrophic factor (BDNF). BDNF plays a central role in neurogenesis, neuronal survival, and resistance to stress-induced damages. Additionally, a

preliminary study revealed that participation in yoga could be beneficial to breast cancer patients and survivors' physical, cognitive and psychological functioning [58].

Conclusion

CRND is a serious and enduring problem that can negatively affect key aspects of cognitive performance, psychosocial functioning, participation in normal activities of daily functioning, and overall quality of life. Despite a growing recognition of its negative effects, interventions to systematically control CRND are still lacking. Successful management of CRND requires the development of effective methods for assess its presence and severity, monitor its clinical course, and test the effectiveness of interventions (e.g., behavioral and pharmacological) to control this debilitating side effect for patients and survivors. To date, however, there exist no gold standard measures of CRND. Consequently, the determination of CRND in cancer control research and clinical services is generally based on a patient's self-reported subjective complaints of cognitive difficulties (e.g., problems in attention and memory performance) and on outcomes of currently available psychometrically validated objective neuropsychological tests. The precision of these methods of assessment is generally debatable.

Despite limitations related to their ecological validity for cancer populations, psychometrically validated objective neuropsychological tests may facilitate a better understanding of the effects of cancer and its treatments on key aspects of cognitive functioning, within the psychological, intrapersonal, relational, and broader contextual circumstances of patients and survivors. Basic neuropsychological screening batteries that include measures of attention, memory, perceptual-motor, intelligence and personality may provide valuable insight into a patient's brain-behavior relationships and indicators of cognitive deficits. Currently available neuropsychological measures can be adapted, standardized and validated for cancer populations. Being able to establish an assortment of reliable neuropsychological batteries of tests that are sensitive to CRND could facilitate more effective screening and complete follow-up evaluation of patients and survivors in oncology research and clinical settings.

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Figure 1.
Multifactorial causal structure of cancer and treatment-related neurocognitive dysfunction.

Table 1

Examples of Neuropsychological Screening and Assessment Measures

Cognitive Domain	Neuropsychological Test
Intelligence	
Verbal	Wechsler Adult Intelligence Scale-Fourth Edition
Non-Verbal	Test of Nonverbal Intelligence - 2nd Edition
Attention	
Simple	Wechsler Adult Intelligence Scale-Digit Span Subtest
Sustained	Conner's Continuous Performance Test
Complex-Visual	Stroop Color Word Test
Complex-Auditory	Paced Serial Addition Test
Processing Speed	
Written	Symbol Digit Modalities Test
Verbal	Animal Naming
Memory	
Verbal Prose Passage	Wechsler Memory Scale-Fourth Edition-Logical Memory
Verbal Word List	Hopkins Verbal Learning Test-Revised
Pictorial	Rey Complex Figure Test
Episodic	Famous Faces
Executive Skills	
Concept Formation	Halstead Category Test
Problem Solving	Tower of London
Inhibition	Go No-Go tasks
Mental Flexibility	Wisconsin Card Sorting Test
Multi-Tasking	Trails Test
Language	
Conversation &	
Expository Speech	^a BDAE-3/Free Conversation; Simple Social Responses
Auditory Comprehension	^a BDAE-3/Complex Ideational Material
Oral Expression	^a BDAE-3/Non-verbal Agility
Visual Naming Ability	Boston Naming Test-2
Motor Function	
Manual Dexterity	Grooved Pegboard
Self-directed Manual Speed	Finger Tapping

^a BDAE-3: Boston Diagnostic Aphasia Examination-3.