Cancer-related cognitive impairment in breast cancer survivors: An examination of conceptual and statistical cognitive domains using principal component analysis

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Abstract

There is a great deal of variability in the composition of neuropsychological test batteries used in the assessment of cancer-related cognitive impairment (CRCI). Not only the development of a gold standard approach for CRCI assessment would allow for easier identification of women suffering from CRCI but it would also promote optimal care for survivors. As a first step towards the development of a valid and reliable unified test battery, the objective of this study was to verify whether the theoretical domains commonly used in CRCI assessment are statistically supported, before and after breast cancer treatment. Principal component analyses (PCA) were performed on the results from 23 neuropsychological tests grouped into eight conceptual domains. For baseline data, the Kaiser-Meyer-Olkin was .82 and Bartlett's $\chi^2(253, N=95) = 949.48$, $P<0.001$. A five-component solution explained 60.94% of the common variance. For the post-treatment data, the Kaiser-Meyer-Olkin was .83 and Bartlett's $\chi^2(253, N=95) = 1007.21$, $P<0.001$ and a five component solution explained 62.03% of the common variance. Although a visual comparison of the theoretical model with those determined via PCA indicated important overlap between conceptual domains and statistical components, significant dissimilarities were also observed.

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Introduction

Background

Breast cancer strikes approximately one in nine women each year.[1] The majority of these women will receive some form of chemotherapy and/or hormonal therapy as part of their treatment regimen. Based on the most recent data, the five-year survival rate for women diagnosed with breast cancer is more than 85%,[1] thereby leading to a significant increase in the number of women living with the long-term side effects of cancer and its treatment. A proliferation of literature on survivors of breast cancer has demonstrated that up to 78% suffer from adverse effects of cancer treatment.[2,3] The decline in cognitive functioning associated with cancer treatment has been often referred to as *chemo-fog, chemo-brain,* or more recently *cancer-related cognitive impairment (CRCI)*; this phenomenon has been well-documented in the literature.[4-9] It is frequently referred to as an invisible malady that has a major impact on an individual's quality of life and everyday functioning.[10]

In order to be effective, chemotherapeutic drugs must be cytotoxic which affects both normal and cancer cells and may account for the cognitive impairment observed in some individuals following chemotherapy treatment.[11] As a result, most researchers and patients tend to associate CRCI with chemotherapy solely.[12] However, there is increasing evidence that hormonal therapy, which is included more often than not in breast cancer treatment (with or without chemotherapy), also has important effects on brain functioning.[13-17] While the literature on the long-term cognitive effects of hormonal therapy is quite sparse compared to that of chemotherapy, the studies that have investigated this question have reported a negative influence of hormonal therapy on cognition in breast cancer patients.[18-20] It has been shown that hormonal therapy can lead to organizational, activational, neurotropic, and neuroprotective deficits in breast cancer survivors.[21] There is substantial evidence that estrogen, which is blocked in hormonal based therapies, modulates cognitive functioning (see Shilling *et al.*[17] for review) and that several regions of the brain that mediate cognition and memory are very rich in estrogen receptors.[22]

Therefore, it is logical that anti-estrogen (hormonal) therapy, that is, the long-term deprivation of estrogen, used in the treatment of breast cancer also plays a role in the cognitive perturbations experienced by breast cancer survivors. Meta-analytic reviews of the literature have revealed that breast cancer survivors experience declines in several cognitive areas such as executive function, verbal memory,[23] language, short-term memory, and spatial abilities.[3,24] Memory and attention deficits seem to be the most frequently reported problems by survivors.[22,25-28] They commonly experience word-finding, tasks-prioritizing, and decision-making difficulties.[12,29,30] Studies have also reported that survivors often feel distressed, anxious, and embarrassed, creating tension and frustration within the family. All of those cancer-related cognitive changes have a direct impact on the life of cancer survivors as it affects both their emotional and functional states.[31]

The assessment of cancer-related cognitive impairment

Despite increasing and convincing evidence that cancer treatment can result in significant impairment in cognitive functioning, various neuropsychological assessment issues complicate the identification and assessment of CRCI. One of the main hurdles comes from the fact that the composition of neuropsychological test batteries and test selection used to evaluate CRCI in cancer survivors varies substantially from one group of researchers to another as no gold standard assessment tool exists in clinical practice.[29,32,33] Other important issues include, but are not limited to, the number of tests administered, the length of the assessment, and the overlap of cognitive functions. While there is general consensus about what tests evaluate specific cognitive functioning, the composition of test batteries is quite varied in CRCI research.[34-37] Because of the lack of standardized neuropsychological test batteries, practitioners are left with the responsibility of selecting instruments that have strong psychometric properties while also matching their clinical objectives. Hundreds of tests are currently available for the conduction of comprehensive neuropsychological evaluations.[38] However, researchers and practitioners do not seem to agree on which tests are *the best ones* to use for CRCI assessment. This lack of consistency across studies leads to great variability in the choice of tests used to represent the various cognitive domains, thereby making comparison of results onerous. And although a substantive literature on test theory and guidelines for the selection of individual tests exists,[39,40] there is a lack of theory specifically addressing the optimal composition of a neuropsychological battery or the choice of tests by cognitive domain. The number and choice of tests administered for the assessment of CRCI can have a significant impact on the results obtained which creates difficulty in accurately identifying the areas of functioning that are most compromised subsequent to cancer treatment and/or in identifying the subgroup of women affected by CRCI.

While these issues arise to a greater or lesser extent irrespective of the presenting problem, they become more salient in areas in which the research findings are inconsistent and the approach to neuropsychological assessment is highly variable across studies (i.e. differences in test selection and composition of cognitive domains) as it is the case in the breast cancer/CRCI research. These obstacles in assessment can eventually be manifested in studies in which the subjective reports from survivors experiencing CRCI do not coincide with objective measures of cognitive function. For example, a 2006 study by Downie, Mar Fan, Tchen, Yi & Tannock[41] measured self-reported quality of life in a group of women receiving adjuvant chemotherapy for breast cancer and compared the results with a neuropsychological measure designed to detect cognitive impairment, the High Sensitivity Cognitive Screen.[42,43] Their goal was to assess whether subjective complaints of cognitive impairment corresponded with objective neuropsychological test results. The authors found discrepancies between the self-reports and the cognitive assessment, particularly in the area of attention and concentration, in that 90% of the patients reported difficulties but only 10% were categorized as abnormal on objective measures. Smaller inconsistencies were also found in the areas of language and memory (78% and 95% self-reported *vs* 61% and 48% identified). They concluded that the High Sensitivity Cognitive Screen may not be sensitive enough to capture the subtle cognitive declines experienced by this population. Our group has also questioned whether a reduced battery could identify individuals vulnerable to CRCI.[44] Using the same subjects and tests described in the study we are reporting here, we showed that a comparable number of the same breast cancer survivors were identified using a subset of nine of the 23 tests.

The current study

Given all the issues related to CRCI assessment and neuropsychological testing mentioned above, it is clear that the development of a consensus about a standard approach to assess residual and lingering effects from cancer and its treatment would have several benefits for the growing population of breast cancer survivors and also for cancer survivorship research in general. Clear, comprehensive, and objective guidelines for CRCI assessment would lead to more reliable and valid results, which would subsequently help to improve the overall quality of life and health outcomes of cancer survivors and their families.[45,46] Additionally, it would allow health care practitioners and researchers to gain a precise and accurate idea of the impact of cancer treatment on the human brain. Redundancy of scales or divergence about their interpretations (*i.e.*, what cognitive domains they assess) may lead to confusion, thereby increasing the risk of misclassification. Misclassification can lead to medical recommendations that are less than optimal or even inappropriate, or a lack of intervention altogether.

However, in determining which tests are the most effective and reliable to use for CRCI detection, it is important to verify whether the theoretical cognitive domains that are currently commonly used in CRCI assessment make sense from a statistical standpoint, that is, that these conceptual domains converge with the ones derived statistically. Consequently, using data obtained from our previous studies on the neuropsychological effects of adjuvant cancer treatment in breast cancer patients,[6,44] the goal of this study was to examine whether the conceptual domains commonly used in CRCI assessment were statistically supported by PCA-based statistical components.[47,48] The second goal was to determine whether cancer treatment had an impact on the statistical components found with PCA.

Method

Participants

The current analyses included breast cancer survivors who underwent chemotherapy and/or hormonal therapy as part of their treatment regimen. Participants were recruited for a larger longitudinal study conducted out of the Ottawa Regional Cancer Centre in Canada investigating the neuropsychological effects of adjuvant chemotherapy. The sample consisted of 95 stage I or II breast cancer patients aged 50 to 66 (M=57.47, SD=4.03), who had undergone mastectomy or lumpectomy, and were receiving chemotherapy (FEC, CEF, AC, AC-Taxol, FAC, AT, or ECT) with or without hormonal treatment (n=49) or hormonal treatment alone (n=46)

which consisted of either tamoxifen or anastrozole. All participants received $50 for each test session they completed.

Sample selection

The study was limited to postmenopausal women aged 66 years or younger as a means of minimizing the potential confounding effects of hormonal status and age-related cognitive decline.[49] Fluency in English was required in order to complete the test battery. Exclusion criteria for all groups included a history of previous cancer and chemotherapy or radiation treatment. Participants presenting with serious psychiatric disorder (*e.g.* major depression, schizophrenia), neurological illness, or significant substance abuse were excluded due to the potential negative effects on cognition. This study was approved by the Human Ethics Board at the Ottawa Hospital and written informed consent was obtained from all participants.

Measures

Table 1 provides a list of the 23 neuropsychological tests that were administered to all of our participants following surgery and before treatment (chemotherapy and/or hormonal therapy) commenced (T1) and again six months later, after treatment had ceased (T2). The tests were chosen in order to depict what is currently used for CRCI detection; they represented the following cognitive domains: visual learning and memory, processing speed, verbal learning and memory, working memory, language function, executive function, motor skills, and visuospatial function. The battery was administered by psychometricians with at least a master's level training in clinical psychology under the supervision of a licensed neuropsychologist.

Procedure

After obtaining informed consent, demographic information and past medical history were collected. Next, the Quick Test[50] was administered to estimate IQ followed by the neuropsychological test battery. All tests were conducted in the same order in both testing sessions (T1 and T2). Sessions lasted an average of three hours and were conducted at either the participant's home or the hospital, according to her preference. Most opted to be seen at home.

Data Analysis

All analyses were conducted using the Statistical Package for the Social Sciences[51]. To determine whether there was statistical support for the conceptual framework underlying the composition of the domains, PCAs were performed on T1 and T2 results. A non-orthogonal (oblimin) rotation was chosen in order to enhance interpretability due to the expected inter-relatedness of the factors. Absolute loadings of 0.4 or higher were used as the loading criterion.[52] We opted against the utilization of a more formal factor analysis technique such as a principal axis factoring or confirmatory factor analysis mostly because the main objective of the present article was to reduce observed data while retaining as much of the original variance as possible.[53,54] Our modest sample size and our desire to minimize reliance on model assumptions were also factors that were taken into account in our decision to use PCA over factor analysis. Yet, we acknowledge that the use of other statistical methods such as factor analysis would allow examining our data from a different angle and would also yield interesting results.

Table 1. Test battery identified by cognitive domain.

Tests	Measure abbreviation
Visual learning and memory	
RVLT Free Recall Trial 1	RVLT, Trial 1
RVLT Long Delay Free Recall Total	RVLT, Long Delay Free
RVLT Long Delay Recognition	RVLT, Long Delay Recog
Family Pictures II from the WMS-III	Family Pictures II
Processing speed	
Digit-Symbol Coding from the WAIS-III	Digit Symbol Coding
Symbol Search from the WAIS-III	Symbol Search
Trail Making Test Part A	Trails A
Verbal learning and memory	
CVLT-II, List A Trial 1	CVLT Trial 1
CVLT-II, Long-Delay Free Recall	CVLT Long Delay Free
CVLT-II, Long-Delay Recognition	CVLT Long Delay Recog
Logical Memory II from the WMS-III	Logical Memory II
Working memory	
Consonant Trigrams	CCC Total
Digit Span from the WAIS-III	Digit Span
Letter-Number-Sequencing from the WAIS-III	Letter-Number Sequencing
Spatial Span from the WMS-III	Spatial Span
Arithmetic from the WAIS-III	Arithmetic
Language function	
Boston Naming Test	Boston Naming Test
Controlled Oral Word Association Test	FAS
Executive function	
PASAT 2.4s, total correct	PASAT
Trail Making Test Part B	Trails B
WCST Trials administered	WCST
Motor	
Grooved Pegboard, D & ND	Grooved Pegboard
Visuospatial function	
Block Design from the WAIS-III	Block Design

PASAT, Paced Auditory Serial Addition Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; CVLT, California Verbal Learning Test; RVLT, Rey Visual Learning Test; WMS, Wechsler Memory Scale.

Table 2. Descriptive statistics of the treatment group.

Descriptive statistics	M(SD)
Age at baseline (years)	57.48 (4.10)
Range	50-66 years
Education (years)	14.18 (3.08)
Range	8-23 years
IQ level	44.25 (3.15)
Range	35-50
Test-retest Interval (days)	151.74 (33.15)
Range	91-245 days

M, mean; SD, standard deviation; IQ, intelligence quotient as measured by the Quick Test (Ammons & Ammons, 1962).

Results

Descriptive statistics relating to age, education, estimated IQ at baseline, and test-retest interval of the treatment group are found in Table 2. Attrition from pre- to post-treatment was less than 10% and, in most cases, was due to subjects declining the retest. Three participants were excluded due to cancer recurrence. Most of the participants had stage I breast cancer, except for five who had stage II disease. Although certain participants only received chemotherapy or hormonal treatment (not a combination of both), the group of women who only received chemotherapy and the group of women who only received hormonal therapy did not significantly differ from each other with respect to either the percentage of women who had begun treatment prior to T1 or days on treatment prior to T1.

We imputed 1.74% of the data using expectation-maximization algorithm. Missing values were typically due to incompletion of a particular test. The data were inspected for univariate outliers and normality and linearity characteristics. The skewness and kurtosis of each variable were within a tolerable range to meet the assumptions of a normal distribution; examination of the histograms also suggested an approximately normal distribution. Examination of the scatterplots showed a linear relationship between all observed variables. No score was more than 3.29 standard deviation units away from its variable mean; therefore no outlier was reported.[52]

Evaluation of the baseline (pre-treatment) data using PCA techniques was associated with a Kaiser-Meyer-Olkin measure of sampling adequacy of .82, considered adequate.[55] The Bartlett's Test of Sphericity was significant ($\chi^2(253, N=95) = 949.48$, $P<0.001$). A five-component solution was found, accounting for 60.94% of the common variance. Details of the variables that were found for each component are included in Table 3.

Individually, the first component accounting for 32.28% of the variance, the second for 9.18%, the third for 7.32%, the fourth for 6.56%, and the fifth component for 5.60%. Components 3 and 4 were identical to the conceptual factors *visual learning and memory* and *verbal learning and memory*. Components 1 and 2 were somewhat consistent with the conceptual factor *working memory* and *processing speed*. Although Component 2 included all of the three tests commonly used to assess *processing speed*, additional tests belonging to three other conceptual domains were also included. Component 5 was difficult to match to a corresponding conceptual domain as it included three tests, each commonly belonging to a different conceptual domain.

Evaluation of the post-treatment data also resulted in a Kaiser-Meyer-Olkin measure of sampling adequacy of .83 and a Bartlett's Test of Sphericity that was significant ($\chi^2(253, N=95 = 1007.21$, $P<0.001$). Similar to the baseline profile, a five-component solution explaining 62.03% of the common variance was found. Details of the variables found for each component are included in Table 3. Individually, the first component accounted for 33.28% of the variance, the second for 9.42%, the third for 7.50%, the fourth for 6.01%, and the fifth component for 5.82% of the common variance. Component 2 was identical to the conceptual factor *verbal learning and memory*. Although Component 4 included two tests belonging to other conceptual domains, it was still somewhat consistent with *visual learning and memory*. Components 3 and 5 were also similar to *processing speed* and *working memory* respectively. Component 1 included a mix of tests belonging to three different conceptual domains thereby making it difficult to find a clear association with a corresponding conceptual domain.

Discussion

As an initial step towards the development of a standard approach to assess CRCI, the major aim of this study was to verify whether the theoretical cognitive domains of a neuropsychological test battery commonly used in CRCI assessments were statistically supported, that is, that the statistical groupings identified through PCAs converged with the theoretical division of tests by domain. We found that at least 60% of the common variance could be accounted for by five of the eight components both before and after treatment, with some overlap between conceptual domains and statistical components. Of the eight theoretical domains, four in particular - visual learning and memory, processing speed, verbal learning and memory, and working memory - showed important degree of overlap with statistically derived components. The remaining four domains - language function, executive function, motor function, and visuospatial function - were more variable.

The conceptual domains *visual learning and memory* and *verbal learning and memory* had the highest degree of overlap with statistically derived components. One reason for this may be that learning and memory are core fundamentals of human cognition and that such domains are less easily disrupted by external events such as cancer treatment.[56] Certain subtests from one conceptual domain were statistically associated with subtests from another conceptual domain. For instance, processing speed was assessed via the subtests Digit Symbol Coding, Symbol Search and Trails A. These remained grouped together in both PCA analyses along with the subtests Trail B, Spatial Span, and Grooved Pegboard. That these subtests were grouped together under one statistical component is not altogether surprising given that speed is a crucial aspect of performance for all of these tests.

At a more basic level, some cognitive functions can be expected to affect all other domains. Executive functioning is an integral part of general cognitive functioning; it is defined as *the capacities that enable a person to engage successfully in independent, purposive, self-serving behavior*[39] and can also influence many other cognitive domains. We found that the tests designed to assess executive function in our conceptual groupings (*i.e.*, PASAT, Trails B, and WCST) were statistically combined with other tests in the PCAs before and after treatment. Almost any neuropsychological test, whether it is intended to assess language, motor function, or other cognitive abilities, requires the development of appropriate strategies and solutions, planning skills, response inhibition, and cognitive flexibility, all abilities commonly associated with executive functioning. It has been argued that most tests are a combination of executive functioning and other cognitive functions; thus the classification of tests into particular cognitive domain could be considered somewhat artificial.[40]

As a result of this complexity in cognitive functioning and the fact that all neuropsychological tests capture multiple facets of cognitive functioning, there are few absolutes when it comes to organizing neuropsychological tests into domains. Different researchers or clinicians may include the same subtests under varying domains depending on their perception of what aspect of cognitive functioning is recruited most by a particular measure. The multiplicity and interrelatedness of cognitive functions thus makes test selection challenging for clinicians and researchers. The results of this study well illustrate this dilemma.

The PCA results before treatment were similar but not identical to the PCA results after treatment which perhaps highlights the impact that the cancer treatment had on the cognitive functioning of our participants. All breast cancer survivors, whether they reported CRCI or not, were included in our study. Given the fact that not all individuals who undergo cancer treatment experience

cognitive deficits afterward, we can assume that certain survivors who do not suffer from CRCI were included in our study. Given that, we can speculate that a greater discrepancy between our pre- and post-treatment results may have been found if we used a cutoff to establish the minimal levels of cognitive symptoms required to be included in the study.

Until quite recently, CRCI was somewhat ignored by the clinical and medical community. The inconsistency and variance found in CRCI research and assessment (discussed earlier) are important contributors to this chemobrain controversy.[57] The emergence of numerous convincing and rigorous studies acknowledging the existence of CRCI have led to a shift in this attitude and it is now generally acknowledge that CRCI can in fact occur in cancer survivors. The results of brain-imaging studies are also starting to unravel the pathophysiologic mechanisms behind CRCI. There have been several reports indicating the existence of brain abnormalities in cancer survivors.[58,59] For example, Kumar *et al*.[60] found cancer-treatment induced necrosis of the brain in more than 66% of the patients. Several magnetic resonance imaging and diffusion tensor imaging studies have also indicated widespread reductions in gray matter volume and white matter connectivity and activation in the brain of cancer survivors.[61-63] According to these studies, CRCI can be explained by the fact that many of the cytostatic agents used today which have smaller molecules and can cross the blood-brain barrier have a direct neurotoxic effect on neurons, glial cells, and/or neurotransmitters.[25,64] This in turn leads to immune system deregulation, DNA damage, and/or hormonal changes such as a decrease in the level of estrogen and progesterone.[65,66]

Additional indications of the existence of CRCI have also been demonstrated via biochemical studies suggesting that cancer treatment contributes to the deregulation of cytokine levels. Cytokines, which are small proteins secreted by the immune system, have been linked to cognitive functioning in a number of research studies.[67-69] One mechanism that has been suggested is that the induction of cytokines in the central nervous system, as triggered by cancer treatment, provokes local inflammation of the brain, espe-

Table 3. Conceptual and statistical factors before and after treatment.

Conceptual domains	Statistical components at baseline (explained 60.94% of common variance)	Statistical components at post-treatment (explained 62.03% of common variance)
Visual learning and memory	*Component 1 (32.28%)*	*Component 1 (33.28%)*
RVLT Trial 1	Digit Span (.82)	PASAT (.75)
RVLT Long Delay Free	Letter-Number Sequencing (.80)	Arithmetic (.72)
RVLT Long Delay Recog	Arithmetic (.79)	WCST (-.68)
Family Pictures II	PASAT (.73)	FAS (.68)
	CCC Total (.71)	
	FAS (.60)	
Processing speed	*Component 2 (9.18%)*	*Component 2 (9.42%)*
Digit Symbol Coding	Trail B (.75)	CVLT Long Delay Free (.84)
Symbol Search	Trail A (.73)	CVLT Long Delay Recog (.84)
Trails A	Symbol Search (-.72)	Logical Memory II (.76)
	Digit Symbol Coding (-.71)	CVLT Trial 1 (.60)
	Spatial Span (-.62)	
	Grooved Pegboard (.56)	
Verbal learning and memory	*Component 3 (7.32%)*	*Component 3 (7.50%)*
CVLT Trial 1	RVLT Trial 1 (-.70)	Grooved Pegboard (.69)
CVLT Long Delay Free	RVLT Long-Delay Free (-.68)	Symbol Search (-.67)
CVLT Long Delay Recog	Family Pictures II (-.67)	Spatial Span (-.65)
Logical Memory II	RVLT Long Delay Recog (-.62)	Trail B (.64)
		Trail A (.62)
		Digit Symbol Coding (-.62)
		Family Pictures (-.46)
Working memory	*Component 4 (6.56%)*	*Component 4 (6.01%)*
CCC Total	CVLT Long Delay Free (-.79)	RVLT Long Delay Recog (-.79)
Digit Span	CVLT Long Delay Recog (-.78)	RVLT Long-Delay Free (-.78)
Letter-Number Sequencing	CVLT Trial 1 (-.72)	RVLT Trial 1 (-.77)
Spatial Span	Logical Memory II (-.48)	Boston Naming Test (-.61)
Arithmetic		Block Design (-.57)
Language function	*Component 5 (5.60%)*	*Component 5 (5.82%)*
Boston Naming Test	Block Design (-.74)	Letter-Number Sequencing (.86)
FAS	Boston Naming Test (-.64)	Digit Span (.86)
	WCST (.56)	CCC Total (.69)
Executive function		
PASAT		
Trails B		
WCST		
Motor		
Grooved Pegboard		
Visuospatial function		
Block Design		

cially in the hippocampus area.[70,71]. This reaction mediates *sickness behavior* such as fatigue, depression, and cognitive changes in cancer patients[72] and may ultimately lead to the clinical presentation of CRCI.[73,74] While this idea is still in its infancy[75] and requires much more research, it provides a plausible mechanistic direction for studying the biological determinants underlying CRCI. In our study, the fact that the results of the post-treatment PCA are different from the results of the baseline PCA might serve as an additional evidence for the existence of CRCI.

Limitations of the study

Certain limitations of our study should be acknowledged. First, the small sample size is an important limitation of our study. While it did satisfy the PCA conditions, based on the Kaiser-Meyer-Olkin test and the communality of each variable, we realize that it met the bare minimum requirement recommended for analyses of this nature. Yet, certain studies have shown that high communalities tend to offset the deleterious effect of small sample size, thereby suggesting that adequate extraction of factors (components) can still be achieved despise small *N*s.[76] Second, the statistically derived components explained a considerable amount, but not all, of the common variance in our data. There are therefore other factors that still need to be identified in our models. Finally, although our data lend statistical evidence to the notion that cancer treatment alters to some degree cognitive functioning after treatment, due to the variability in neuropsychological batteries employed by different researchers, there are limits to the generalizability of the current study.

Conclusions and future directions

Our findings show that certain conceptual grouping of subtests commonly used in CRCI assessment has reasonable statistical support. However, additional research is required in order to quantitatively and objectively examine the grouping of subtests and perhaps re-evaluate what groupings are the most optimal way to proceed for CRCI detection. Furthermore, the differences between our pre- and post-treatment results demonstrate that cancer treatment changes the distribution of neuropsychological tests across conceptual domains. This lends statistical evidence to the notion that cancer treatment alters to some degree cognitive functioning after treatment.

It would be important that future studies explore the potential risk factors for CRCI and evaluate other malignancies in this context; most CRCI studies have focused on breast cancer survivors. Furthermore, since the development of appropriate assessment tools for CRCI heavily relies on our ability to accurately define the specific mechanisms underlying CRCI, it is crucial to continue high-quality studies on CRCI. Collaborative work toward the development of appropriate intervention strategies aimed at improving the quality of life of individuals suffering from CRCI can only be fully developed once the exact nature of the deficits is clarified, and sensitive screening tools are available to identify those affected. Poignant examples in the literature of the daily impact of CRCI on quality of life[77,78] serve as a reminder of the importance of continued research in this area.

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