Breast Cancer: Basic and Clinical Research

ORIGINAL RESEARCH

The Relationship between Visuospatial Memory and Coping Strategies in Breast Cancer Survivors

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Abstract:

Background: In the US there are over 2.5 million breast cancer survivors (BCSs), most of whom have required some type of intensive treatment. How individuals cope with the treatment process may relate to why neurocognitive problems arise.

Method: We explored the impact of treatment for breast cancer (BC) on performance of the Memory Island task, both on working memory and on the general index of cognitive performance in relation to coping strategies of BCSs compared to age-matched controls.

Results: The evidence obtained suggests a reduced performance in visuospatial memory in BCSs. Those who used emotional coping strategies displayed reduced performance in visuospatial learning and immediate memory. Those women who used problem-focused coping strategies performed better in those tasks measuring psychomotor speed, general intelligence, and delayed visuospatial memory.

Conclusions: It is concluded that further investigation of the relationship between coping strategies and performance on visuospatial tasks may provide useful information on residual levels of neurocognitive deficits and psychosocial adaptation in BCSs.

Keywords: breast cancer survivors, Puerto Rican, emotion-focused, problem-focused, visuospatial memory, Memory Island

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Introduction

Investigations conducted by the American Cancer Society indicate that there are 2.5 million breast cancer survivors (BCSs) in the United States. This means that 1 out of 8 women can expect to be diagnosed with some form of breast cancer (BC) at some point in their life.[1,2] Among Puerto Rican women, BC is the most commonly diagnosed type of cancer, accounting for 33% of all cancer diagnoses from 1999 to 2003.[3] Statistics from the Division of Epidemiology of the Department of Health of Puerto Rico indicate that approximately 1,540 women are diagnosed annually and that the survival rate of these women is 76.4%.[2,3] Consequently, understanding the long-term consequences of BC and its treatments becomes an important challenge for health-care providers.

Chemo-brain and chemo-fog are the colloquial terms used to describe the phenomenon of cognitive decline that some patients may experience after chemotherapy.[4,5] It has mainly been studied in BC patients because of their high survival rate as well as in younger and middle-aged women who complain of cognitive decline. Several investigations have shown impairments in visuospatial learning and memory following chemotherapy in long-term cancer survivors.[6–9] Animal studies also indicate the existence of impairments in the performance of spatial learning and memory tasks following treatment with methotrexate or 5-fluorouracil, the most commonly used chemotherapy agents.[10–12]

Chemotherapeutic agents are administered in period cycles, orally or intravenously. The chemicals move through the bloodstream, destroying malignant cells in different phases of their growth.[13] However, anything that is poisonous to cancer cells may also be poisonous to other, healthy, cells in the body. Researchers have hypothesized that the toxicity of chemotherapy drugs can affect blood vessels and eventually cross the blood-brain barrier, allowing high concentrations of chemicals to reach several cortical brain areas.[9] Although the neurotoxicity mechanisms leading to cognitive deficits are not well understood, evidence suggests that those chemicals used in chemotherapy for BC may induce negative effects on the brain tissue and neurotransmitters involved in cognitive processing.[14–16]

Findings regarding cognitive impairment in women with a history of chemotherapy are inconsistent, indicating that several neuropsychological domains such as, attention and, spatial ability, visual memory, and working memory, are affected by high and even standard doses of chemotherapy.[16] Studies on BCSs have reported cognitive impairment as long as 5 to 10 years after completion of chemotherapy.[17–20] In addition, women who received chemotherapy and Tamoxifen (hormonal treatment), scored lower in visual memory and verbal working memory.[21] Considering the complications and cofounders involved in studying BCSs, pre-clinical models are vital to understand the possible side effects of chemotherapy, including neurocognitive impairments.

Most of the standardized neuropsychological tests used to assess chemotherapy's impact on long-term working memory and visual spatial memory[8,19] are not translatable to pre-clinical models. As the Morris water maze is the most commonly used and recognized pre-clinical learning and memory animal task, a translation and validation of a human version of a visuospatial memory task, such as Memory Island (MI),[22,23] is necessary. Correlations between MI and other standardized tests suggest that it encompasses motor coordination, picture recognition, visual working memory, and visuospatial memory.[22,24] MI can be an appropriate measure of visuospatial learning and memory suitable for use in other cultures. MI adequately assesses depth perception, visuospatial attention, figure-ground discrimination, spatial perception, and orientation. Furthermore, MI tasks can be utilized as a quantitative and qualitative measure that mimics pre-clinical assessments.

BCSs often experience physical, emotional, and social difficulties that can prolong psychological stress due to the impact of the disease and its treatment during the remission period.[25–27] Stress emerges from an imbalance between the requirements of the environmental situation and the person's ability to cope with that situation.[28] According to the transactional model of stress and coping, stress is conceptualized as the appraisal induced by the interaction between an individual and the environment when confronted with situations that exceed the individual's resources.[29,30] The theory states that cognitive appraisal and coping strategies are the processes that mediate those

stressful transactions (individual-environment) and therefore will determine the immediate and long-term perception and reactions toward a stressful situation. The person first recognizes a stressful situation as troublesome (primary appraisal); next, the person evaluates and determines what resources are required in order to overcome or handle the problem (secondary appraisal). The individual engages in cognitive and behavioral attempts to reduce, minimize, or tolerate the internal and external demands of the appraised transaction.[29]

The process of coping has two major functions: dealing with the problem that is causing the stress (problem-focused) and regulating emotional states (emotion-focused). The aim of problem-focused strategies is to cope with stress by acting directly on its cause; such strategies usually consist of an individual's attempting to resolve or alter the source of their stress by removing or alleviating the stressor. Some examples of problem-focused strategies are active coping, planning, suppression of competing activities, and restraint.[31] On the other hand, emotion-focused coping strategies are directed toward reducing or managing the emotional distress associated with a stressful situation. These strategies predominate when people appraise a situation as something that must be endured.[28] Some examples of emotion-focused strategies are positive reinterpretation, denial, acceptance, use of emotional social support, and turning to religion.[31]

In a longitudinal study, coping strategies were assessed in women who had completed chemotherapy for BC from 4 weeks to 4 months prior to the assessment.[32] The results demonstrated that participants utilized acceptance, religion, and distraction as their primary coping strategies.[32] This suggests that they incline toward using emotion-focused strategies as being the more effective strategies in dealing with psychosocial situations soon after completing chemotherapy. Understanding and knowing what coping strategies have been engaged by cancer survivors will enhance the development and outcomes of cognitive-behavioral treatments, improving mental health and general well-being.[33,34]

Culturally, there are differences among the types of coping strategies that BCSs of different minority groups use in order to manage stressful situations.[35] Studies indicate that Latina BCSs tend to use more spiritual styles of coping and have a greater need for social support.[36–38] Researchers highlight the importance of further understanding the psychological aspects of coping that are necessary to managing and reducing emotional distress in BCSs.[35] Nevertheless, there appears to be insufficient information available on Hispanic patients regarding what coping strategies are more effective in dealing with the long-term consequences of chemotherapy treatment, and which strategies can have a direct impact on a given survivor's overall quality of life.[36]

Method

Participants and recruitment

The data collected was part of Dr. Summer Acevedo's research project titled "Effect of ApoE on Spatial Learning and Memory in Hispanic Cancer Survivors" and sponsored by the Moffitt Cancer Center. A total of 38 participants from an existing data base were analyzed. The sample consisted of 16 BC women in remission (at the time of the study) who had received chemotherapy and 22 women who had either never been diagnosed with BC or who had not received chemotherapy. The identities of the subjects were maintained in strict confidentiality following HIPAA guidelines and regulations. Release-of-information consent was approved by the Ponce School of Medicine Institutional Review Board. Prospective participants between 30 to 65 years of age were contacted at health fairs, cancer support groups, and Relay for Life annual walks, sponsored by the American Cancer Association, at various locations in Puerto Rico. An interviewer contacted the individuals interested in the study in order to complete a telephone questionnaire and determine their eligibility. To be eligible, the BCSs must have concluded chemotherapy for non-metastatic BC at least six months prior to the study. Any woman with a history of a major psychiatric disorder, a neurological or medical disease, or a severe vision or hearing impairment was excluded from the investigation. Information regarding demographics, level of education attained, duration of illness, and type of chemotherapy received was gathered if inclusion criteria were fulfilled. Follow-up phone calls were also made to arrange an evaluation date. Socio-demographic information and level of education were

matched with women who were not diagnosed with any type of cancer.

Procedures

All neurocognitive testing was conducted by research assistants. Participants were tested in a single visit that lasted approximately two hours. The evaluations were conducted in a designated clinical room at the Psychoneurometrics Research Building at the Ponce School of Medicine. Ten-minute breaks between tasks were authorized at the discretion of each subject. Participants were allowed to end the evaluation or leave the project at any moment.

Conners' Continuous Performance Test (CPT-II)

For the non-verbal computerized attention task, respondents were required to press the space bar when any letter except the target letter X appeared.[39] The CPT-II software program measures response time, omission and commission errors, change in reaction-time and consistency.[39] The software contains large normative samples, including clinical data on ADHD sufferers and neurologically impaired adults. The results, based on T-scores and percentiles and relative to both the general population (non-clinical sample) and an ADHD clinical sample, were recorded. Automatically generated scoring sheets were printed out for analysis after CPT II administration. The non-clinical score was used as an overall measure of attention.

Grooved Pegboard Test (GPT)

In order to measure psychomotor speed, the Grooved Pegboard Test was administered. The task consists of placing 25 pegs in a linear order into their corresponding holes in the least amount of time possible. The individual's execution time is measured twice, once while using the dominant hand and once using the non-dominant hand.

Family pictures

To examine visuospatial learning and memory, the Family Picture subtest of the Wechsler Memory Scale was administered.[40] A portrait that includes six family members (mother, father, grandmother, grandfather, daughter, son, and a dog) is shown at the beginning of the task while instructions are given. Subsequently, four scenes are presented for 10 seconds each, allowing the examinee to learn important aspects about the image, such as appearing members, their corresponding positions and what they are doing. After a 30 minute delay, the individual is encouraged to recall the information without viewing the picture. A cumulative percentage of the information remembered from both trials is then obtained.

Novel Image/Novel Location (NINL)

Novel Image/Novel Location is a visuospatial task that requires recognition of various natural and man-made objects/images.[22] The subject is presented with a series of 12 panels, each containing three pictures in four quadrants (A, B, C, and D), for eight seconds each. The images are all similar in complexity, but different in content. The subject is asked to remember the images on each panel as well as the position of each image on the panel. Immediately after, subjects are presented with a series of 12 new panels. These new panels will either be identical to or have some slight variation compared to their counterparts in the first set. Each new panel may contain a variance in the positioning of one of the three images (novel location), or one of the three images may be different (novel image). The subject is asked to identify the new panel as either being identical to or containing a change in comparison to the first-viewed panel; in the latter case, the subject is asked to identify the change. This test was developed and copyrighted by Dr. Jacob Raber at Oregon Health and Science University.

Selected sub-tests of the Wechsler Adult Intelligence Scale-III, adapted Spanish version

The scores of seven selected sub-scales of the Wechsler Adult Intelligence Scale (EIWA-III for its initials in Spanish) were used to obtain the Working Memory Index (WMI) and prorated Full Scale Intelligence Quotient (FSIQ).[41] The Working Memory Index was assessed by performance on the Arithmetic, Digit Span, and Letter-Number Sequencing sub-tests. The execution in these tasks depends upon the individual's cognitive ability to assemble, hold, and manipulate information while performing a wide range of tasks, including comprehending, reasoning, and learning, in order to formulate an adequate response.[42,43]

A prediction of an FSIQ from the EIWA-III was made using four selected sub-scales: Vocabulary and Similarities from the Verbal Scale and Block Design and Matrix Reasoning from the Performance Scale. Sums for standard scores were made independently for the Verbal and Performance sub-tests. The averages of the standard scores were multiplied by six for the Verbal Scale and by five for the Performance Scale. The multipliers are the total number of sub-tests on each scale respectively. The two prorated standard scores were summed, and the resulting value was converted to Full Scale IQ using Table A.4 in appendix A of the EIWA-III manual.[44]

Memory Island

The Memory Island (MI) is a virtual reality task based on the Morris water maze (Morris, 1985), created to assess visuospatial learning and memory.[22,24,45] As is the case with the traditional pre-clinical water maze, the MI virtual reality task has learning (visible), immediate-memory (hidden), and delayed-memory (probe) trials. The computer-generated virtual test consists of an island comprising of four quadrants that contain different target items. The participants navigate through the virtual island using a joystick while listening to nature sounds through a headphone (eg, birds singing, water flowing). During the visible portion of the task, participants are instructed to navigate the virtual island's four quadrants in order to find different objects located next to large flags poles with brightly colored flags (Fig. 1). In the hidden trials, participants are asked to find (four times) one of the targets from the first set of trials, without the aid of a flag. If the participants are unable to locate the target after two minutes, an arrow appears at the top of the screen to guide them to the appropriate target. It is important to affirm that the initial performance, or first two minutes of the task, is the most appropriate measure of learning and memory (Fig. 1). Consequently, performance was examined based on cumulative distance (virtual units/seconds) to the target during the first two minutes in the learning (visible) and immediate-memory (hidden) trials. After 15 minutes, a 30-second delayed-memory (probe) trial was assessed using time spent in the target quadrant, consistent with previous studies. For the Puerto Rican population, the script and word prompts were translated to Spanish and modified to employ culturally appropriate language. Permission for the use of this program was obtained from Jacob Raber, Ph.D., who is a Professor in the Department of Neurology at Oregon Health and Science University.

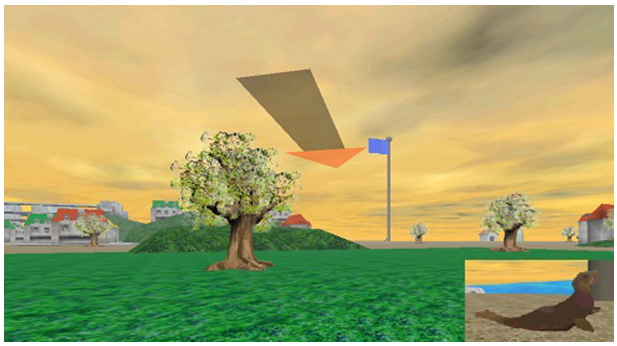

Figure 1. Memory Island visible screen shots. A representative picture of the seal target (with the flagpole) that appears during the visible trial; the arrow appears at the top of the screen after two minutes.

COPE inventory

To assess the coping strategy most frequently used in the last year, a 60-item inventory was administered in Spanish.[31,46–48] The responses were presented in a 4-point scale and ranged from 1 (I usually don't do this at all) to 4 (I usually do this a lot) covering 10 different coping tactics (eg, active coping, denial, planning). The scale was divided into two different ways of coping, emotion-focused and problem-focused strategies, with five coping tactics in each cluster.

Statistical analysis

Analyses were conducted using SPSS software, version 17.0. A Fisher's exact test was used to obtain an age distribution within groups. The Student's *t* test was used to explore differences between cognitive performances within groups (BCSs and women without diagnoses) in standardized assessments (GPT, CPT, Working Memory Index, Prorated FSIQ, SRE, and Cope Inventory). A Repeated Measure (REM) Analysis of Variance (ANOVA) was conducted to evaluate (across trials) the participants' velocity and performance (cumulative distance to target) during the visible and hidden trials of the MI tasks. The Wilcoxon signed rank test was used to test the median differences (in the probe performance) between the percent of time spent in the target quadrant and all other quadrants. For all analyses, $P < 0.05$ was considered statistically significant.

In order to further explore the relationship between neurocognitive performance and the effects of chemotherapy in BCSs, Step-wise multiple linear regression analysis were used to adjust by age and psychosocial stress, age and problem-focused coping strategies, or age and emotion-focused coping strategies. The adjusted partial correlation coefficients and the determination coefficients were used as measures of association.

Results

Study population

Table 1 contains the Socio-demographic information, number of years post-chemotherapy, type of treatment, and number of treatment cycles received within the BCS group. The sample consisted of 16 BCSs and 22 participants who had not received chemotherapy for BC or any other type of cancer. The age range of all of the participants was 30 to 64 years. BCSs mean age was 52.5 ± 2.0, and non-BCSs mean age was 46.7 ± 3.8. All participants were female Puerto Ricans who were well educated and, primarily, employed at least part-time. The average time-lapse since BCSs had received chemotherapy was 5.6 ± 1.1 years. Within the BCSs group, all participants received standard-dose chemotherapy for at least 3 weeks and up to 6 months. The median number of cycles of chemotherapy ranged from 1 to 6 months with an average of 3.3 ± 0.6 cycles. Approximately 60% of BCSs received hormone replacement therapy (Tamoxifen) as part of their treatment.

Group differences in neurocognitive performance

The results obtained from the comparison of the performance of non-BCSs versus BCSs on measures of neurocognitive functioning are included in Table 2. No significant differences were obtained when comparing performance between the groups on measures of sustained attention (measured with CPT), picture

Table 1. Sample characteristics.

	Non-breast cancer	Breast cancer survivors	*P*
N	22	16	
Age	46.7 ± 3.8	52.5 ± 2.0	0.10
Years of education	16.1 ± 0.7	15.3 ± 0.6	0.41
Percentage right-handed	86.4%	100%	0.08
Smokers	4.3%	0%	0.42
Employment status			0.85
Unemployed	26.3%	27.3%	
Employed	73.7%	72.7%	
Marital status			0.43
Married	42.1%	64.3%	
Single	31.6%	28.6%	
Divorced	26.3%	7.1%	
Income			0.12
<$25,000 a year	33.3%	72.7%	
<$35,000 a year	26.7%	9.1%	
>$35,000 a year	40.0%	18.2%	
Length of chemotherapy (months)		1.0 ± 0.3	
Doses/cycle		3.3 ± 0.6	
Years post-chemotherapy		5.6 ± 1.1	
Hormone treatment (tamoxifen)		60%	
Types of chemotherapy			
Adriamycin only		25.0%	
Adriamycin and cytoxan		56.2%	
Methotrexate		6.2%	
Unknown chemotherapy		12.6%	
Chemotherapy and radiotherapy		12.6%	

Note: Mean ± SEM.

Table 2. Neurocognitive measures and psychosocial stress in non-breast cancer and breast cancer survivors.

Neurocognitive measures	Non-breast cancer	Breast cancer survivors	*t*	*P*
Attention				
CPT—overall non-clinical score	45.5 ± 3.23	48.7 ± 4.37	0.44	0.57
Percentage ADD/ADHD	0.41 ± 0.1	0.38 ± 0.1	1.00	0.83
Psychomotor speed				
Grooved Pegboard Test—dominant	68.4 ± 1.8	80.9 ± 5.1	–2.31	0.02*
Grooved Pegboard Test—non-dominant	78.9 ± 1.8	86.6 ± 5.7	–1.05	0.16
Visuospatial learning and memory				
Family Pictures total score	89.1 ± 3.8	77.8 ± 6.2	0.46	0.13
NINL Novel Image	11.5 ± 0.9	10.2 ± 1.4	–0.04	0.43
NINL Novel Location	11.0 ± 1.0	9.19 ± 1.5	0.33	0.48
NINL total Score	54.5 ± 2.6	48.8 ± 3.0	0.82	0.16
EIWA-III selected sub-scales				
Arithmetic	11.1 ± 0.5	10.2 ± 0.6	0.58	0.25
Digit Span	15.8 ± 4.0	12.4 ± 0.9	1.15	0.60
Letter-number sequencing	12.0 ± 0.5	11.0 ± 0.7	1.51	0.28
Working Memory Index (EIWA-III)	110.3 ± 2.6	111.3 ± 3.6	–0.05	0.82
Vocabulary	12.0 ± 0.5	11.6 ± 0.7	1.16	0.64
Similarities	12.7 ± 0.4	11.7 ± 0.9	1.24	0.22
Block design	10.6 ± 0.6	10.7 ± 1.1	–0.38	0.93
Matrix reasoning	15.2 ± 4.0	10.5 ± 0.9	1.07	0.48
Prorated FSIQ (EIWA-III)	110.4 ± 2.2	107.7 ± 5.0	0.54	0.59

Notes: Mean ± SEM; *$P < 0.05$, statistically significant.
Abbreviations: CPT, Conners' Continuous Performance Test; FSIQ, Full Scale IQ; EIWA-III, Wechsler Adult Intelligence Scale for Adults, Third ed.

recognition, visuospatial learning, or memory tasks (NINL, Family Pictures). However, statistically significant differences in GPT means were observed, indicating a reduced psychomotor speed performance in BCSs ($P < 0.02$) as compared to the non-BCSs control group.

Selected sub-scales of the Wechsler Adult Intelligence Scale (EIWA-III) were administered to both groups in order to determine whether there were cognitive performance differences within groups. Student's *t* tests indicated that there were no differences in the WMI or individual sub-tests (arithmetic, digit span, letter-number sequencing); nor were any differences found in the prorated FSIQ composite (vocabulary, similarities, block design, matrix reasoning) or individual sub-tests.

In order to identify possible group difference in the average velocity in the visuospatial learning (visible trials) and immediate-memory (hidden trials) sections of the MI, a Student's *t* test was used. The results indicated that there were no differences between groups on the average velocity (virtual units/sec) in either the visible ($P = 0.48$) or the hidden trials ($P = 0.51$). A Repeated Measure (REM) Analysis of Variance (ANOVA) assessing performance using cumulative distance to target in the first two minutes was used across trials to examine learning differences between BCSs and non-BCSs. Our findings indicate that there were no differences across the visible trials in average cumulative distance to the target ($F = 1.72$, $P = 0.47$, Fig. 2A–B). The performance during the visible trials did improve as indicated by significant effects within the trial ($F = 34.0$, $P < 0.001$, Fig. 2A). The results indicate that BCSs were able to learn how to navigate to the fourth target, which improved performance over the trials to a level similar to that of the non-BCSs participants.

During the hidden portion of the task, the subjects were asked to find the same target over four trials. A REM ANOVA for cumulative distance to the target across trials indicated that there were differences between groups in overall performance ($F = 4.48$, $P < 0.05$, Fig. 2B, D), particularly in trial three ($P < 0.05$, Fig. 2A). In the hidden trials, both groups demonstrated that practice resulted in improvements ($F = 41.31$, $P < 0.0001$, Fig. 2A).This data suggests that BCSs display reduced immediate-memory performance; however, their performance improved over the course of the trials.

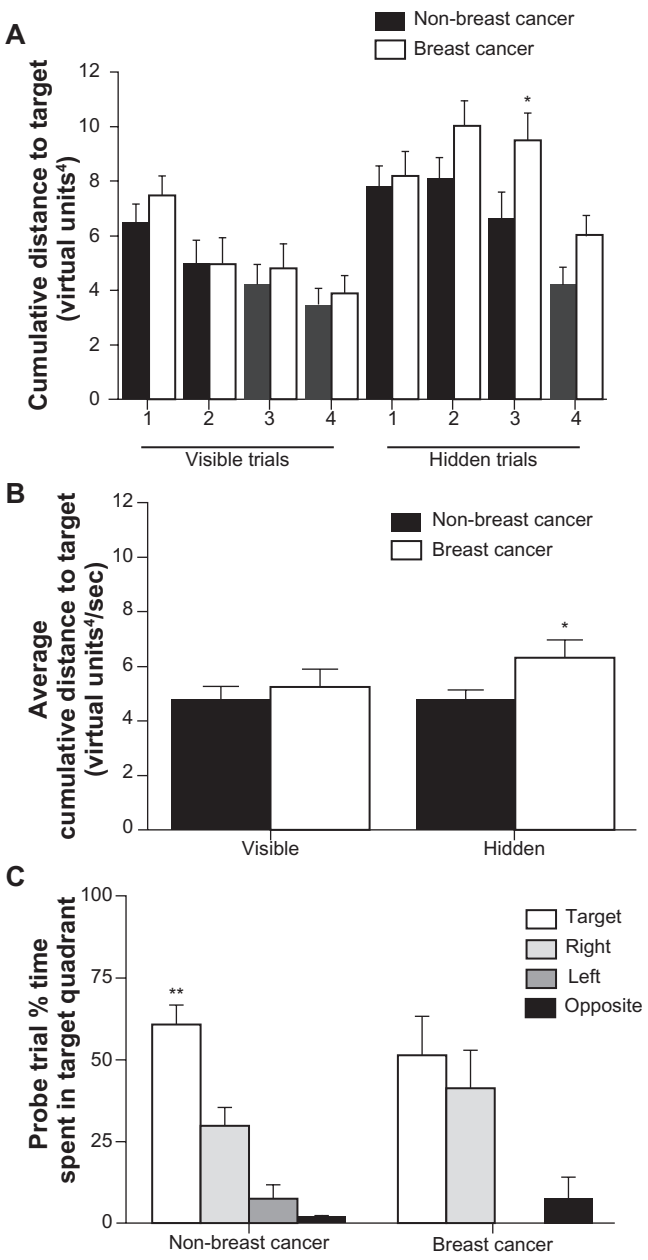

Figure 2. Differences in Memory Island performance between non-BC and BCSs. **A**) There were no differences in performance between groups during the visible trials. **B**) BCSs accumulated a higher than average cumulative target displacement during the hidden trials (*$P < 0.05$). **C**) Non-BC subjects spent more time in the target quadrant during the probe trial (**$P < 0.01$ target vs. all other quadrants). BCSs did not spend more time in the target compared to the right quadrant.

After 15 minutes of the last hidden trail, delayed memory (probe trial) was assessed for thirty seconds. According to the results obtained by the Wilcoxon signed rank test, the non-BCSs spent more time in the target quadrant during the delayed-memory (probe) trial ($P < 0.00$, target vs. all other quadrants, Fig. 2C). However, the BCSs who had undergone chemotherapy did not spend more time in the target quadrant compared to the right quadrant (Fig. 2C), with only 50% of subjects displaying target quadrant preference ($P < 0.04$, Fig. 2C). T-tests indicate that 82% of Non-BCs preferred the target quadrant (spent more than 50% of time in the target quadrant) with only 50% of the BC subjects displaying target quadrant preference ($P < 0.04$). Overall, our data show that participating BCSs who had undergone at least one month of chemotherapy experienced visuospatial memory impairments in the virtual reality MI task.

The analysis of the Spearman's correlation demonstrates strong associations between the MI task and other cognitive measures. The results indicate a highly significant association between the learning trial of MI and the Family Pictures total score ($P < 0.007$), as indicated in Table 3. The learning portion of the virtual reality task also correlates with other cognitive measures from the EIWA-III scale such as digit span, block design, matrix reasoning, WMI, and FSIQ. The immediate-memory portion of the task correlates with the EIWA-III in terms of the digit-span, block-design, and matrix-reasoning subscales. Moreover, the delayed-memory task correlated with GPT (dominant hand and non-dominant hand), Family Pictures, NINL Image, NINL Location, and NINL total score. The results yield statistically significant correlations between the MI's delayed-memory task and the EIWA-III sub-scales such arithmetic, block design, matrix reasoning, and FSIQ.

Relationship between coping strategies and neurocognitive performance in breast cancer survivors

According to the Student's *t* tests analysis performed, there is a statistically significant difference between the means obtained for both groups in the COPE inventory. The results reveal that the BCSs present higher denial-based coping strategies compared to non-BCSs ($P = 0.05$), as shown in Table 4. Non-statistically significant trends towards higher levels of active coping, positive reinterpretation, and overall emotion-focused composite scores were detected in BCSs.

When analyzing the results of the emotional coping composite and problem-focused composite within

Table 3. Spearman's correlations between Memory Island and other cognitive and neuropsychological measures.

Neurocognitive measures	Visible cumulative distance to target	Hidden cumulative distance to target	Probe % time in target quadrant
Attention			
CPT—overall non-clinical score	0.11 (0.52)	0.18 (0.29)	–0.24 (0.16)
Psychomotor speed			
Grooved Pegboard test—dominant	–0.06 (0.73)	0.17 (0.30)	–0.38 (0.02)*
Grooved Pegboard test—non-dominant	0.26 (0.13)	0.13 (0.46)	–0.44 (0.009)**
Visuospatial learning and memory			
Family Pictures total score	–0.45 (0.007)**	0.20 (0.22)	0.57 (<0.001)***
NINL Novel Image	–0.27 (0.10)	–0.02 (0.93)	0.38 (0.03)*
NINL Novel location	–0.01 (0.94)	–0.15 (0.39)	0.39 (0.03)*
NINL Total Score	–0.24 (0.15)	–0.26 (0.13)	0.41 (0.02)*
EIWA-III selected sub-scales			
Arithmetic	–0.25 (0.16)	–0.25 (0.11)	0.54 (0.003)**
Digit span	–0.35 (0.04)*	–0.35 (0.04)*	0.02 (0.89)
Letter-number sequencing	0.05 (0.78)	0.05 (0.78)	0.04 (0.84)
Working Memory Index (EIWA-III)	–0.45 (0.01)**	–0.23 (0.21)	0.08 (0.67)
Vocabulary	–0.22 (0.20)	–0.05 (0.78)	0.21 (0.24)
Similarities	–0.24 (0.15)	–0.20 (0.22)	0.20 (0.26)
Block design	–0.36 (0.03)*	–0.36 (0.03)*	0.64 (<0.001)***
Matrix reasoning	–0.39 (0.02)*	–0.40 (0.02)*	0.43 (0.01)**
Prorated FSIQ (EIWA-III)	–0.36 (0.04)*	–0.11 (0.52)	0.40 (0.02)*

Notes: Correlation coefficient (*P* value); *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, statistically significant.
Abbreviations: CPT, Conners' Continuous Performance Test; FSIQ, Full Scale IQ; EIWA-III, Wechsler Adult Intelligence Scale for Adults, Third ed.

all participants, significant correlations between neurocognitive measures were found. These also indicate that the performance on the MI correlate with implemented coping strategies. Therefore, those women who performed worse during the learning (average visible, $P < 0.02$) and immediate-memory (average hidden, $P < 0.007$) trials had a tendency to implement emotion-focused coping strategies. Examining the individual emotional sub-scales of the COPE Inventory, only denial increased in BCSs, which also correlated with lower immediate-memory performance in MI (average hidden: Correlation Coefficient, 0.50, $P < 0.003$).

As illustrated in Table 5, those women who tended to perform better in the delayed-memory (probe) trial had a tendency to implement problem-focused coping strategies ($P < 0.01$). A statistically significant correlation was observed between the problem-focused coping strategy and GPT ($P = 0.05$). Both the planning (probe: Correlation Coefficient, 0.41, $P < 0.02$) and the restraint (probe: Correlation Coefficient, 0.42, $P < 0.02$) sub-scales individually correlated to increased delayed-memory performance. Furthermore, those women with an average prorated FSIQ reported higher scores in the problem-focused coping strategies ($P < 0.03$), particularly in the planning subscale (Correlation Coefficient, 0.42, $P < 0.02$). No significant differences were seen in the attention, WMI, or other visuospatial learning and memory tasks (NINL, Family Picture).

Additionally, Step-wise multiple linear regressions were generated in order to examine the correlation between women with history of BC who received chemotherapy and cognitive measures adjusted by age and emotional coping or problem coping strategies. Only one significant relationship between problem focused coping and reduced performance in the GPT with their dominant hand in BCSs was observed ($P < 0.03$). This suggests there is a 9.99% chance that reduced psychomotor speed performance in BCSs was due to chemotherapy. No statistical significance was observed between women who received chemotherapy and other neurocognitive measures with respect to age or coping strategies used.

Table 4. Mean differences in coping strategies of non-breast cancer and breast cancer survivors.

Coping strategies	Non-breast cancer	Breast cancer survivors	*P*
Problem-focused			
Active coping	12.3 ± 0.3	13.4 ± 0.5	0.06
Planning	13.4 ± 0.4	13.4 ± 0.5	0.91
Suppression of competing activities	9.9 ± 0.4	10.7 ± 0.5	0.24
Restraint	11.1 ± 0.6	10.0 ± 0.7	0.22
Use of instrumental social support	12.0 ± 0.7	13.1 ± 0.5	0.21
Total	59.1 ± 1.6	60.7 ± 1.6	0.51
Emotion-focused			
Use of emotional social support	11.1 ± 0.7	11.8 ± 0.5	0.49
Positive reinterpretation and growth	12.8 ± 0.5	14.0 ± 0.5	0.09
Acceptance	11.3 ± 0.5	11.6 ± 0.7	0.69
Denial	5.9 ± 0.4	7.6 ± 0.8	0.05*
Religious coping	12.9 ± 0.8	12.8 ± 1.0	0.93
Total	53.7 ± 1.1	57.8 ± 7.7	0.08
Other scales			
Mental disengagement	9.2 ± 0.4	9.4 ± 0.5	0.82
Behavioral disengagement	6.5 ± 0.4	7.1 ± 0.6	0.40
Focus on and venting of emotions	10.8 ± 0.6	10.0 ± 0.6	0.34
Humor	9.0 ± 0.6	8.3 ± 1.0	0.54
Substance use	5.0 ± 0.6	4.1 ± 0.1	0.21

Notes: Mean ± SEM; *$P < 0.05$, statistically significant.

Discussion

In the present study, different neuropsychological domains were assessed in order to explore whether chemotherapy and/or radiation treatment have a detrimental effect on cognitive performance in long-term BCSs. The results from the MI tasks (reduced performance in immediate and delayed memory) suggest that BC treatment (chemotherapy and/or radiation) might induce cognitive deficits in BCSs. Using analyses similar to those employed in pre-clinical rodent models of the quadrant-based water maze, we examined performance during learning, immediate memory, and delayed (15 minutes) memory in MI. Our data indicate the BCSs who had undergone treatment were able to learn the MI task. However, survivors displayed mild impairments in the immediate memory compared to controls, though improving their performance with multiple trials. Only 50% of

Table 5. Spearman's correlations between coping strategies among neurocognitive measures.

Neurocognitive measures	Emotion-focused coping strategy	Problem-focused coping strategy
Grooved Pegboard test		
Dominant hand	0.20 (0.22)	–0.21 (0.21)
Non-dominant hand	0.11 (0.51)	–0.32 (0.05)*
Attention (CPT)	0.17 (0.29)	0.29 (0.07)
Memory Island		
Visible	0.40 (0.02)*	–0.19 (0.26)
Hidden	0.45 (0.007)**	–0.03 (0.87)
Probe Target	–0.11 (0.54)	0.52 (0.002)**
Family Pictures total	–0.27 (0.11)	0.29 (0.08)
NINL Total		
Working Memory Index (EIWA-III)	–0.16 (0.36)	0.17 (0.35)
Prorated FSIQ (EIWA-III)	–0.29 (0.07)	0.36 (0.03)*

Notes: Correlation coefficient (*P* value); *$P < 0.05$; **$P < 0.01$, statistically significant.
Abbreviations: CPT, Conners' Continuous Performance Test; EIWA-II, Wechsler Adult Intelligence Scale for Adults, Third ed., FSIQ, Full Scale Intelligence Quotient.

the BCSs navigated close to the target in the delayed memory trial compared to 82% of the healthy non-BC subjects. Our evidence mimics the animal studies, which also demonstrated immediate and delayed memory impairments in the water maze.[10–12] Though this is a small pilot study, our data supports further investigations using tasks such as MI in order to validate the effects of pre-clinical testing of chemotherapy agents on long-term cognitive deficits.

Some studies reported mild to moderate levels of impairment in attention in BCSs.[20,49,50] However, the absence of differences among groups in our study is similar to other reported findings.[18,50,51] The results obtained in the EIWA-III for the verbal WMI and the prorated FSIQ yield no differences in performance between groups. The absence of intragroup differences is probably due to small sample size or to other confounding factors. In addition, there was no indication of age effects in our sample on any assessment according to multiple linear regressions.

With regards to the most prevalent coping strategies used by BCSs, our study employed the COPE inventory.[30,46–48] Consistent with other studies, trends towards higher levels of active coping, positive reinterpretation and growth, and overall emotion-focused composite scores were obtained from BCSs.[32,34] No differences were observed in religious coping strategies among groups. This may be explained by the fact that members of most Latin-American cultures are heavily influenced by religious beliefs and frequently resort to religion as a means of dealing with stressful situations.[32] Literature regarding coping mechanisms in Latin BCSs indicates that these individuals have very high levels of religiosity and spirituality, which have been shown to be related to greater levels of overall well-being.[52] In terms of problem-focused coping, only active coping was found to be slightly greater in BCSs. However, this was not found to be highly significant. Therefore, survivors showed a predominantly emotion-focused style of coping.

Women who implemented emotion-focused strategies showed a decrease in learning and immediate visuospatial memory performance, whereas those who engaged in problem-focused strategies displayed greater memory retention in the delayed-memory trial of MI. Furthermore, the results of this exploratory study indicate a slower psychomotor speed in BCSs when they used their dominant hands. Those women who demonstrated reduced motor-speed performance on the GPT showed a tendency to employ problem-focused strategies according to the linear regressions. The reduced psychomotor speed was not necessarily indicative of poor performance, but rather may reflect a more cautious approach.

Although it was not qualitatively accounted for during testing sessions, we can infer that the neuropsychological battery was interpreted as a stressful situation by participants due to its novelty and complexity.[53] According to our findings, we can speculate that those women with a tendency to utilize problem-focused coping strategies were able to attempt and execute cognitive tasks in a stepwise fashion. They were able to handle the complexity of the tasks at hand by inhibiting other activities. This approach facilitated initiation and planning strategies, allowing them to perform better in neurocognitive tasks. However, those who are more inclined to engage in emotional coping strategies (eg, denial) probably need more time to structure and execute a plan in order to deal with stressful situations. We can hypothesize that those with a tendency to emotionally cope with stressful situations might display difficulties concentrating and rapidly processing new information and therefore will display lower scores in neurocognitive tasks.[53]

We confronted several limitations. In the current investigation, the sample size of both groups was small, probably affecting some of the statistical analyses performed. We did not account for information regarding premorbid cognitive functioning before, during, or immediately after chemotherapy exposure, and this may be a concern for other sources of variability. Information regarding genetic risk factors in cognitive deficits such as the presence of apolipoprotein E (apoE) allele 4 was not integrated in our data analyses due to the insufficient number of participants. Previous studies indicate that those BCSs who are apoE4 carriers demonstrate increased memory deficits after chemotherapy compared to non-carrier cancer survivors.[54] The use of a larger sample may result in other associations between neurocognitive measures and stress and coping strategies that were not observed in this study.

For future investigations, a longitudinal study would be appropriate in order to explore the impact of various cancer treatment modalities

such as a high or standard dose of chemotherapy, radiotherapy, or hormonal treatment; which can also be compared with breast cancer patients who did not received any treatment. All of the EIWA-III sub-scales available in the neuropsychological battery could be used in order to reassess the statistical significance of the FSIQ prorated composite. Furthermore, the use of MI should be further validated in order to examine the long-term effects on general cognitive performance and visuospatial learning and memory in cancer survivors. Also, it would be important to include additional tasks that assess executive functions and some verbal learning and memory tasks in order to explore other neuropsychological domains that were not considered for in this study.

As individual differences were not accounted for in our analysis, it would be valuable to correlate neuropsychological scores with possible structural changes among frontal, parietal and temporal association areas utilizing human brain imaging.[54,55] Results of past investigations utilizing magnetic resonance diffusion tensor imaging in combination with detailed cognitive assessment indicate reduced white matter integrity in frontal and parietal regions in BC patients compared with healthy control or non-chemotherapy treated patients.[54] It is important to further evaluate the associations between coping strategies and neurocognitive measures to better improve cognitive functionality and therefore quality of life. This may be accomplished by gathering qualitative information in order to understand how psychosocial stress is perceived and what coping strategies are being employed by long-term BCSs. This may lead to the exploration of specific factors and potential mechanisms related to the effects of chemotherapy agents in neurocognitive functions and their impact on psychological well-being in long-term cancer survivors. Future research should replicate this study with subjects of different ethnicities to determine the generalizability of these findings.

Our results showed mild to moderate impairment in visuospatial memory and reduced motor-speed performance in BCSs. This exploratory study may provide the first evidence that suggests that MI may be an appropriate task to further assess the cognitive effects of chemotherapy on visuospatial memory in BCSs, allowing for the detection of problems that can interfere with daily living and identifying individuals who could benefit from therapeutic interventions such as neurocognitive rehabilitation. This battery of tests can be further developed to assess the utility of different neurocognitive therapies on the recovery of BCSs.

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Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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