Cuadernos de Neuropsicología / Panamerican Journal of Neuropsychology
2021, Vol. 15 Nº2 150 - 164

ISSN: 0718-4123
DOI: 10.7714/CNPS/15.2.212

Traumatic symptomatology and cognitive functioning in women with breast cancer treated with chemotherapy: An exploratory study

Síntomatologia traumatica y funcionamiento cognitivo en pacientes con cáncer de mama tratados con quimioterapia: Estudio exploratorio

Sintomatologia traumática e funcionamento cognitivo em pacientes com cancro da mama tratados com quimioterapia: Estudo exploratório

RECIBIDO: 25 septiembre 2020 ***ACEPTADO: 31 mayo 2021***

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Palavras-chave: *cancro da mama; sintomatologia traumática; funcionamento cognitivo; quimioterapia; estudo transversal.*

A B S T R A C T

Objective: The purpose of this study was to explore the associations between traumatic symptomatology and impairments on cognitive functioning, in a sample of women with breast cancer, in treatment with chemotherapy. **Methods**: Participants were 20 women diagnosed with breast cancer (*M*age = 48.40; *SD* = 8.98). In this exploratory cross-sectional study, a battery of neuropsychological tests was used to evaluate the participants' cognitive functioning, as well as a measure for traumatic symptomatology. **Results:** The results showed that 35% of the participants experienced traumatic symptomatology at clinically significant levels (cut-off > 35.5). Furthermore, significant correlations ($p < .05$) were found between traumatic symptomatology and executive functioning, particularly cognitive flexibility. **Conclusion:** Although exploratory in nature, our findings highlight the need to screen for traumatic symptomatology in breast cancer patients, regardless of treatments for oncological disease, and the need to develop interventions targeting these traumatic symptoms in order to prevent the development of cognitive deficits. during tasks that involve cognitive and motivation control processing.

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ISSN: 0718-4123
DOI: 10.7714/CNPS/15.2.212

R E S U M E N

Objetivo: El propósito de este estudio fue explorar las asociaciones entre la sintomatología traumática y las alteraciones en el funcionamiento cognitivo, en una muestra de mujeres con cáncer de mama, en tratamiento con quimioterapia. **Métodos**: Las participantes fueron 20 mujeres diagnosticadas de cáncer de mama (Mage = 48,40; SD = 8,98). En este estudio transversal exploratorio, se utilizó una batería de pruebas neuropsicológicas para evaluar el funcionamiento cognitivo de las participantes, así como una medida de sintomatología traumática. **Resultados:** Los resultados mostraron que el 35% de los participantes experimentaron sintomatología traumática a niveles clínicamente significativos (corte > 35,5). Además, se encontraron correlaciones significativas ($p < 0,05$) entre la sintomatología traumática y el funcionamiento ejecutivo, en particular la flexibilidad cognitiva. **Conclusiones:** Aunque de carácter exploratorio, nuestros hallazgos ponen de manifiesto la necesidad de realizar un cribado de la sintomatología traumática en pacientes con cáncer de mama, independientemente de los tratamientos de la enfermedad oncológica, y la necesidad de desarrollar intervenciones dirigidas a estos síntomas traumáticos para prevenir el desarrollo de déficits cognitivos. durante las tareas que implican un procesamiento cognitivo y de control de la motivación.

R E S U M O

Objetivo: Este estudo pretende explorar a associação entre sintomatologia traumática e défices no funcionamento cognitivo em mulheres com cancro da mama, em tratamento com quimioterapia. **Método**: Os participantes são 20 mulheres diagnosticadas com cancro da mama (*M*idade = 48.40; *SD* = 8.98). Neste estudo transversal exploratório foram aplicados vários testes neuropsicológicos para avaliar o funcionamento cognitivo das participantes, bem como um questionário para avaliar a sintomatologia traumática. **Resultados**: Os resultados mostram que 35% das participantes apresentaram sintomatologia traumática clinicamente significativa (ponte de corte > 35.5). Foram encontradas várias correlações significativas entre esta sintomatologia traumática e o funcionamento executivo, sobretudo em termos de flexibilidade cognitiva. **Conclusões**: Apesar da sua natureza exploratória, os resultados deste estudo mostram a importância de avaliar a sintomatologia traumática nas mulheres com cancro da mama e a necessidade de desenvolver intervenções que trabalharem estes sintomas traumáticos de forma a prevenir o desenvolvimento de défices cognitivos.

Introduction

Cancer has become a major public health problem (Sikora & Timbs, 2004) and it is currently considered a chronic disease with high rates of morbidity and mortality (Phillips & Currow, 2010). Breast cancer is one of the most common type of tumors in the industrialized world and among women (IARC, 2012). Cancer diagnostic and, consequently, the associated treatments can be a source of intense psychological suffering, not only for the patients, but also for their families (Akechi et al., 2006; Surbone et al., 2010). Breast cancer can be a stressful event causing significant changes and losses in different areas, with impact on patients' quality of life (Oh et al., 2004). These stressors include the abrupt and unpredictable character of the course of the disease, feelings of uncontrollability, the diversity, duration and secondary effects of treatments and the expectations regarding future physical trauma, such as the loss of the breast, that may significantly influence the onset of traumatic symptomatology or even Posttraumatic Stress Disorder (PTSD) in cancer patients (Costanzo et al., 2007; Hahn, Hayes, Kahn, Litwin, & Ganz, 2015; Pasquini & Biondi, 2007; Perez & Galdón, 2002). The first manifestation of traumatic symptoms often appears suddenly posing a threat to the physical integrity of the cancer patient (Perez & Galdón, 2002).

Previous studies have shown that the incidence of PTSD among cancer patients can range from 10% to 32% (Elklit & Blum, 2011; Mehnert, Berg, Henrich, & Herschbach, 2009; Naidich & Motta, 2000). This range may be explained by the methodological diversity of the studies, as well as by the differences among participants' sociodemographic and clinical characteristics (e.g., age at the diagnosis, education, socioeconomic status, type of cancer, type of treatments, stage of cancer, and time since treatment end) (Wu, Wang, Cofie, Kaminga, & Liu, 2016).

More recently, attention has been given to the patients' cognitive changes observed during the course of the disease due to patients' complaints regarding cognitive functioning after the end of treatments and when they return to their daily life or to their work. This is also supported by the findings of studies showing that some cancer patients present significant changes in cognitive functioning (Anderson-Hanley et al., 2003; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Wefel et al., 2011). Some empirical evidence suggests that these changes in cognitive functioning can result from the neurotoxic effects of chemotherapy (Ahles, Root, & Ryan, 2012; Schagen et al., 2002; Shilling & Jenkins, 2007; Vearncombe, Rolfe, Wright,

ISSN: 0718-4123
DOI: 10.7714/CNPS/15.2.212

Pachana, Andrew, & Beadle, 2009). Studies involving women with breast cancer additionally showed that these patients tend to experience more difficulties in cognitive functioning not only during chemotherapy, but also some months later, in comparison to age-matched non-cancer women (Loh et al., 2016). Studies with cancer patients found that the most affected cognitive domains are attention, memory, executive functions, and processing speed (Bender et al., 2007; Kesler, Kent, & O'Hara, 2011; Palmer, Trotter, Joy, & Carlson, 2008; Wefel & Schagen, 2012). Specifically in breast cancer patients, Reuter-Lorenz and Crimprich (2013) found problems with memory, concentration, or other cognitive abilities, which may represent significant barriers to the recovery of family dynamics, as well as professional and social roles. Moreover, these problems can affect patients' quality of life and compromise their adaptation to the disease and to their daily routines (Boykoff, Moieni, & Subramanian, 2009; Janelsins, Kesler, Ahles, & Morrow, 2014).

Although the side effects of cancer treatments are often cited as the main explanatory mechanism for these cognitive changes, studies did not always find support for this explanation. For instance, several studies evidenced that cancer patients experience cognitive impairment even before the cancer-related treatments (Andreotti, Root, Ahles, McEwen, & Compas, 2014; López-Santiago, Cruzado, Custodio, & Feliú, 2011, Vardi, 2009). This cognitive impairment was observed especially in terms of executive functions (with 30% of participants being below the normative data). Variables such as lower levels of education, age, genetic factors, and advanced stage of the disease were associated with lower cognitive performance. Also, a lower cognitive reserve (i.e., a decrease in psychomotor speed and short-term verbal ability), greater mental health vulnerability (e.g., anxiety, depression, stress disorders or sleep disorders), as well as the emotional impact of the diagnosis and its implications (e.g. menopause, personality traits and fatigue) may be influencing cognitive performance before cancer-related treatments (Ahles et al., 2012, Rubio, Sirgo, Forcadell, Mele, & Guma, 2009; Vardy, Wefel, Ahles, Tannock, & Schagen, 2008).

One important variable that has been pointed out as a potential explanatory factor to cognitive deficits found in cancer patients is stress. When faced with the diagnosis of cancer, patients have to deal with existential anxiety (involving death concerns) (Andreotti et al., 2014). According to Crimprich (1992), these existential concerns may impoverish patients' cognitive resources explaining the observed cognitive deficits. Moreover, as stated previously, patients in the presence of a life-threating disease, such as cancer, may develop PTSD. This disorder has been linked to cognitive deficits both in terms of executive functions and verbal learning, memory, and attention (Aupperle, Melrose, Stein, & Paulus, 2012; Scott et al., 2015; Stein, Kennedy, & Twamley, 2002; Yehuda, Golier, Halligan, & Harvey, 2004). In one study, patients with primary brain cancer were assessed before and 3-months after radiotherapy. The authors found that patients experienced deficits in cognitive performance before and after radiotherapy. Additionally, concerning cognitive deficits, 17% of the participants also experienced clinically significant levels of PTSD before radiotherapy and 13% of them continued to experience PTSD after radiotherapy (Kangas, Tate, Williams, & Smee, 2012). In another study with cancer patients, a positive relationship between cognitive impairment and PTSD symptoms was also found, even before starting any cancer-related treatment. This seems to suggest that cancer-related PTSD symptoms can influence patients' cognitive performance (Hermelink et al., 2015).

Considering that breast cancer can be a potentially traumatic experience, which has several consequences for the patients, it is important to examine the association between traumatic symptomatology and cognitive functioning among women with breast cancer beyond chemotherapy. Thus, the aims of the present study were (1) to analyze the prevalence of clinically significant traumatic symptoms; (2) to analyze the prevalence of deficits in different areas of cognitive functioning; and (3) to explore the associations between levels of traumatic symptomatology and cognitive performance in different areas of cognitive functioning (attention, memory, processing speed, and executive functions).

Method

Participants

A convenience sample was recruited through a non-probabilistic sampling process, being composed by a group of women diagnosed with breast cancer. The sample was collected at a Breast Cancer Support Center located in the north of Portugal between September 2016 and January 2017. Inclusion criteria were (1) have a diagnosis of breast cancer, (2) undergo chemotherapy treatment, (3) have 18 years old or being older, (4) know how to read and write in Portuguese, and (5) being physically and cognitively able to complete the evaluation protocol. Exclusion criteria included (1) have another cancer diagnosis, (2) be in a terminal stage, and (3) have a history of alcohol or drugs abuse. One of the participants did not complete all the evaluations due to worsening health status, and, for that reason, was excluded from analyses. A total of 30

ISSN: 0718-4123
DOI: 10.7714/CNPS/15.2.212

women with breast cancer were contacted. From these, 20 accepted to participate. Their age varied between 37 and 66 years old (*M* = 48.40, *SD* = 8.98). Most of the participants were married, have a higher education, were employed, have an annual income that varied between € 7.000 and € 80.000, and lived with the nuclear family (see Table 1).

Table 1
Sociodemographic characteristics of the participants (N=20)

Variables	**n (%)**
Civil Status	
Single	2(10.0)
Married	15(75.0)
Divorced/Separated	3(15.0)
Education	
2nd cycle	1(5.0)
3rd cycle	1(5.0)
High school	1(5.0)
Higher education	17(85.0)
Annual income (in €)	
Until 7.000	1(5.9)
Between 7.000 and 20.000	7(41.2)
Between 20.000 and 40.000	6(35.3)
Between 40.000 and 80.000	2(11.8)
Above 80.000	1(5.9)
Household	
Herself	2(10.0)
Herself and the partner	6(30.0)
Herself and children	1(5.0)
Nuclear family	10(50.0)
Extended family	1(5.0)

Most of the participants were diagnosed in 2015. Most of them had a stage III cancer. The majority (85%) did not present metastases. All participants, at the beginning of the study, had already begun oncological treatments. At the time of data collection, 85% of the participants were undergoing hormone therapy. Regarding the diagnosis of psychological/psychiatric illness, 10% of the sample had a medical diagnosis of anxiety, 15% of depression and 15% of comorbid diagnosis of depression and anxiety (see Table 2).

Table 2
Clinical Characteristics of the Sample (N = 20)

Variables	***n (%)***
Year of diagnosis	
2010	2(10.0)
2011	3(15.0)
2012	1(5.0)
2013	2(10.0)
2014	3(15.0)
2015	5(25.0)
2016	4(20.0)
Disease stage	
Stage II	8(47.1)
Stage III	9(52.9)
Treatments already done	

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DOI: 10.7714/CNPS/15.2.212

Surgery	19(95.0)
Chemotherapy	20(100.0)
Internal radiotherapy	4(20.0)
External radiotherapy	12(60.0)
Hormonotherapy	17(85.0)
Immunotherapy	4(20.0)
Treatment at the beginning of the study	
Treatment interruption (due to pregnancy)	
Remission	1(5.0)
Treatment with hormone therapy	
Combined treatment (immunotherapy and radiotherapy or chemotherapy)	2(10.0)
	15(75.0)
	2(10.0)

Measures

Sociodemographic and clinical questionnaire. Data on demographic and medical history were collected.

Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997; Portuguese version by Rocha et al., 2016). This is a self-report measure that evaluates the subjective suffering associated with the potential traumatic situations faced by the individual. It includes 22 items that assesses the severity of PTSD symptoms experienced in the previous week. The Portuguese version of the total scale presents good internal consistency. In the present sample, the Cronbach's alfa for the total scale was .95, and for the subscales were: $\alpha_{avoidance}$ = .80; $\alpha_{intrusion}$ = .85; $\alpha_{hypervigilance}$ = .81. A cut-off-point of 35.5 is used to identify clinically significant traumatic symptomatology (probable case of PTSD) (Rocha et al., 2016).

Wechsler Adult Intelligence Scale–Third Edition (WAIS-III; Wechsler, 1997; Portuguese version by Rocha, 2008). This battery is a clinical instrument for individual application composed by 14 subtests that evaluates the adolescents' and adults' intelligence. WAIS-III grouped subtests allow to assess multiple domains of cognitive functioning and possible deficits. Battery subtests have good reliability metrics with internal consistency values ranging between .74 and .95. This battery of tests has been applied in studies that include cancer participants (e.g., Wefel et al., 2004).

Behavioral Assessment of the Dysexecutive Syndrome (BADS; Wilson, Alderman, Burgess, Emslie, & Evans, 1996). This instrument was developed to use information about daily tasks to evaluate executive functions (Strauss, Sherman, & Spreen, 2006). It is structured in six subtests, with tasks simulating real-life activities. It was developed to assess deficits, not only in executive functioning in general, but also in specific components of executive functions (planning, inhibition, cognitive flexibility). For the present study, only two subtests were used, namely 'zoo map' and 'search for keys'. In the Portuguese population this test presents internal consistency values of .41 (Barbosa, Peixoto & Silveira, 2011).

Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay & Curtiss, 1993). This test was originally developed to evaluate abstract reasoning and the ability to modify cognitive strategies in response to changes in environmental situations (Strauss, Sherman & Spreen, 2006). It can be considered a measure of executive function since it assesses the skills to develop and maintain problem solving strategies, cognitive flexibility, and the ability to use feedback in solving problems. The WCST presents good psychometric qualities with Cronbach's alphas ranging between .72 and .90 (De la Cruz, 2001).

Trail Making Test (TMT; Reitan, 1992). This test is part of the battery of Halstead-Reitan neuropsychological tests. It is divided into two parts: part A (TMT A) and part B (TMT B). In the first part, subjects are asked to connect the numbers from 1 to 25 that are scattered on the sheet. In the second part, the subjects are asked to alternate numbers (1 to 13) and letters (from A to M). In both parts of the test the result obtained corresponds to the time (in seconds) spent in each test. Test time is converted into scalar scores, where 10 is the average score (equal to or greater than 10 within the normative sample). This test can provide information about processing speed, attention, mental flexibility, as well as executive functioning, and is also sensitive to the detection of a possible cognitive impairment (Cavaco et al., 2015) being suitable for using with cancer patients (Wefel, Saleeba, Buzdar, & Meyers, 2010).

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DOI: 10.7714/CNPS/15.2.212

Rey Complex Figure Test (Rey, 1942). This is a test composed of a complex, geometric, and abstract figure. The application encompasses two moments: in the first one, the subject is asked to copy the figure in much detail as possible. Subsequently, after three minutes, the subject is asked to draw the same figure without the stimulus, remembering the parts that he/she did previously. In both phases, the aim is to analyze the way individual perceives the data provided and what was retained spontaneously by the memory. This test has also been used to evaluate perceptual activity and visual memory (Fernando, Chard, Butcher, & McKay, 2003), being equally suitable for use with cancer patients (Schagen et al., 2002).

The Stroop Color and Word Test (SCWT; Golden & Freshwater, 1994). It evaluates basic psychological processes, namely cognitive flexibility, selective attention, and resistance to interference, through the evaluation called the "Stroop effect", which consists in the inhibition of automatic responses in favor of other more unusual. This test has three categories: reading, naming, and interference. The scores obtained in each category are converted into a standardized scale in t-scores (M = 50; SD = 10), where anyone with a t-score ≥ 50 is considered within the normative sample, and whoever has the inverse is considered below normality. The Portuguese version has good internal consistency (α = .663; Fernandes, 2013).

Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964; Portuguese adaptation by Cavaco et al., 2015). This test is used to evaluate the processes of learning, memory evocation and recognition. It is effective in identifying the basic principles related to the retention process of new information (Rabin, Barr, & Burton, 2005). It consists of 15 words list that is read aloud to the subject with a span of seconds between words, for five consecutive times. Each attempt is followed by spontaneous evocation. The raw scores of each word repetition are converted into scalar scores in which the mean value is 10 (equal to or greater than 10 is within the normative sample).

Benton Visual Retention Test (BVRT; Benton, 1963). This neuropsychological instrument is used to evaluate visual processing, visual memory and visuoconstructional skills (Burin, Drake, & Harris, 2007). It consists of three shapes (C, D and E), which have the same level of difficulty, and each one consists of ten blades with geometric figures. Each form can be administered in four different ways, standardized by the author (administrations A, B, C and D). The form C, type A, was used consisting in presenting each card to the participant for 10 seconds, requesting the immediate memory reproduction. As this instrument is not validated for the Portuguese population, the validated Spanish version of the test was used in the present study. This version presents good reliability indicators, with values of internal consistency ranging between .74 and .84 (Benton, 2002).

Procedure

To accomplish the study aims all ethical principles established for conducting research with human beings were fulfilled. Before participants' recruitment, the study was approved by the ethics committee of the Breast Cancer Support Center. The research project dissemination was carried out by the center, by the researchers through informational sessions, as well as through leaflets and social networks. Interested and available participants were contacted by one of the researchers with the intention of scheduling the first session for presenting the study, gathering the informed consent, and conducting the interview. The research protocol was implemented over three sessions, each lasting an average of 1.5 hours. The scheduling of these sessions was conducted according to the participants' availability. In the first session, participants were informed about the study aim, procedures, and confidentiality. After signing the informed consent, the sociodemographic and clinical data of the participants were collected. At the end of the session, the self-report questionnaires were completed, to evaluate the participants' mental health status. In the second and third sessions, neuropsychological tests were administered.

Data Analysis

Data analyses were performed using the software SPSS (IBM - Statistical Package for the Social Sciences – v.21). Prior to the implementation of the statistical analyses to accomplish each aim, data normality and homogeneity were assessed through Kolmogorov-Smirnov and Levene tests, respectively. As the assumptions for the use of parametric tests were not met, nonparametric equivalents were used. To describe the likely prevalence of PTSD symptoms (clinically significant levels of traumatic symptomatology) and cognitive impairment in different domains (attention, memory, processing speed, and executive functions) frequency analyses were used. To describe patients' cognitive functioning, standardized scores were

ISSN: 0718-4123
DOI: 10.7714/CNPS/15.2.212

considered, except for the test on the Search for Keys and RAVLT 30 minutes, in which the raw scores were used. Sperman's Rho correlation coefficients were computed to explore the associations between PTSD symptoms and performance in the neuropsychological tests.

Results

Considering the cutoff-point on the IES-R, 7 (35%) participants showed clinically significant levels of PTSD symptomatology (see Table 3).

Table 3

Descriptive data of IES-R total score and their different subscales – total and according to the presence or absence of PTSD

Scale	***Mean***	***SD***	***Min***	***Max***	***M***	***SD***	***M***	***SD***
					Without PTSD		***With PTSD***	
IES-R Total	28.35	15.98	5	66	19.15	9.00	45.43	11.09
IES-R Avoidance	1.19	.75	0	2.88	.78	.43	1.96	.59
IES-R Intrusion	1.34	.82	.13	2.75	.90	.55	2.14	.61
IES-R Hypervigilance	1.35	.81	.17	3.50	.95	.48	2.10	.79

As can be seen in Table 4, women showed cognitive deficits namely in attention (sustained, divided, and alternating), verbal processing speed, long term verbal and short-term visual memory and executive functions (cognitive flexibility and inhibition). No deficits were found on motor processing speed, short-term verbal memory and executive functions (updating and planning).

Table 4

Performance in neuropsychological evaluation tests (N=20)

Area of Cognitive Functioning		**Neuropsychological Tests**	**With deficit N (%)**	**Without deficit N (%)**
Attention	**Sustained**	STROOP Color	**13(68.4)**	6(31.6)
		TMT A	**12(63.2)**	7(36.8)
	Divided/ Alternating	TMT B	**15 (78.9)**	4(21.1)
		STROOP Color/Word	7 (36.8)	12(63.2)
		WAIS-Letters and numbers	3(15.0)	17(85.0)
Processing Speed	**Verbal**	STROOP word	**12(63.2)**	6(31.6)
	Motor	WAIS-Symbol search	1(5.0)	19(95.0)
		WAIS- code	4(20.0)	16(80.0)
	Short-term verbal	WAIS-Digits memory	6(30.0)	14(70.0)
		AVLT 1	8(42.1)	11(57.9)
	Long-term verbal	AVLT 30 minutes	**11(57.9)**	8(42.1)

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DOI: 10.7714/CNPS/15.2.212

Memory	**Short-term visual**	Benton Total Correct Reproductions	3(15.8)	16(84.2)
		Expected errors	3(15.8)	16(84.2)
		Rey-Osterrieth Complex Figure - memory	**12(63.2)**	7(36.8)
Executive Functions	**Updating**	WAIS Inverse Digits Memory Letters and numbers	6 (30.0)	14 (70.0)
		Arithmetic	3(15.0)	17(85.0)
		Similarities		
		Matrices	9(45.0)	11(55.0)
			1(5.0)	19(95.0)
			2(10.0)	18(90.0)
	Planning	Search for keys	0 (0)	19(100)
		Zoo map	1(5.3)	18(94.7)
	Inhibition	STROOP Color/Word	7 (36.8)	12(63.2)
		TMT B	**15(78.9)**	4(21.1)
Executive Functions (continuation)	**Cognitive flexibility**	WISCONSIN No of total errors	**11(57.9)**	8(42.1)
		Perseverative answers	**12(63.2)**	7(36.8)
		Perseverative errors	**12(63.2)**	7(36.8)
		Non-perseverative. errors	9(47.4)	10(52.6)
		No. of complete categories	2(10.5)	17(89.5)
		No. of cards to complete 1st category	3(15.8)	16(84.2)
		Failure to maintain criteria Learn	8(42.1)	11(57.9)
		STROOP Interference	5 (26.3)	14 (73.7)
			4 (21.1)	15 (78.9)

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DOI: 10.7714/CNPS/15.2.212

Correlations are presented in Table 5. A significant correlation was found between avoidance (IES-R) and participants' performance in the symbols survey (WAIS-III), used to evaluate the processing speed, with higher avoidance symptoms being associated with slow processing speed. Statistically significant correlations were also found between PTSD symptoms (IES-R total) and the Wisconsin test performance (letters applied, total number of errors, perseverative responses, perseverative errors, non-perseverative errors). Higher PTSD symptoms were also associated with higher cognitive inflexibility.

Significant correlations between avoidance (IES-R) and the Wisconsin test performance (applied charts, total number of errors, perseverative responses, perseverative and non-perseverative errors, number of complete categories) were also found. Higher levels of avoidance were associated with higher cognitive inflexibility. Intrusion thoughts (IES-R) were significantly associated with the Wisconsin test (applied letters, total number of errors, perseverative responses, and perseverative errors): higher levels of intrusion were associated with higher cognitive inflexibility. Finally, the results showed significant correlations between hypervigilance (IES-R) and the Wisconsin test (letters applied, total number of errors, perseverative responses, perseverative and non-perseverative errors): higher hypervigilance was also associated with higher cognitive inflexibility.

Table 5

Correlations between the IER-S scale and the respective subscales and the performance in the different neuropsychological test using the non-parametric Spearman's Rho test

Area of Cognitive Functioning		**Neuropsychological Tests**	**IES-R Total** ***r(p)***	IES-R Avoidance ***r(p)***	IES-R Intrusion ***r(p)***	IES-R Hypervigilance ***r(p)***
Attention	Sustained	STROOP Color	-.159 (.515)	-.053 (.829)	-.164 (.504)	-.136 (.579)
		TMT A	-.007 (.977)	.128 (.601)	.140 (.568)	.053 (.830)
	Divided/ Alternating	TMT B	.073 (.768)	.220 (.365)	.088 (.720)	.005 (.982)
		STROOP Color/Word	.025 (.920)	-.013 (.957)	.140 (.568)	-.024 (.921)
		WAIS-Letters and numbers	.071 (.774)	.138 (.573)	-.065 (751)	-.078 (751)
Processing Speed	Verbal	STROOP Word	-.048 (.844)	-.041 (.867)	-.096 (.696)	.030 (.904)
	Motor	WAIS-Symbol search	-.415 (069)	**-.446 (049)**	-.357 (.123)	-.435 (055)
		WAIS- Code	-.210 (.375)	-.272 (.245)	-.162 (.495)	-.178 (.452)
	Short-term verbal	WAIS-Digits memory	-.100 (.675)	-.043 (.856)	-.101 (.671)	-.155 (.514)
		AVLT 1	-.062 (.801)	.079 (.748)	-.062 (-.299)	-.295 (-.373)
	Long-term	AVLT 30 minutes	-.242 (.318)	-.251 (.300)	-.299 (.214)	-.373

ISSN: 0718-4123
DOI: 10.7714/CNPS/15.2.212

	verbal					(.116)
Memory	Short-term Visual	Benton Total Correct Reproductions	.018 (.942)	-.143 (.558)	.032 (.897)	.055 (.822)
		Total errors	-.151 (.537)	.053 (831)	-.185 (.447)	-.097 (.692)
		Rey-Osterrieth Complex Figure - Memory	.415 (.077)	.171 (.483)	.368 (.121)	.354 (.137)
Executive Functions	Updating	WAIS Inverse Digits Memory	.087 (.714)	.145 (.542)	.049 (.839)	.034 (.888)
		Letters and numbers	.071 (.774)	.138 (.573)	-.065 (.751)	-.078 (.751)
		Arithmetic	-.035 (.884)	-.194 (.412)	-.076 (.751)	-.051 (.830)
		Similarities	-.005 (.984)	-.163(.493)	.111 (.642)	-.071 (.765)
		Matrices	-.067 (.780)	-.288 (.219)	.174 (.462)	-.237 (.314)
Executive Functions (continuation)	Planning	Search for keys Total	-.070 (.776)	-.003 (.991)	-.024 (.923)	.044 (.858)
		Zoo Map	-.356 (.135)	-.294 (.221)	-.166 (.497)	-.352 (.140)
	Inhibition	STROOP Color/Word	.025 (.920)	-.013 (.957)	.140 (.568)	-.024 (.923)
		TMT B	.073 (.768)	.220 (.365)	.088 (.720)	.025 (.982)
		WISCONSIN No of letters applied	**.484 (.036)**	**.532 (.019)**	.451 (.052)	**.476 (.039)**
		Correct Answers	.309 (.198)	.380 (.108)	.203 (.404)	.380 (.190)
		No of total errors	**.552 (.013)**	**.536 (.018)**	**.551 (.014)**	**.570 (.011)**
		Perseverative answers	**.591 (.008)**	**.574 (.010)**	**.513 (.025)**	**.599 (.007)**

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Cognitive flexibility	Perseverative errors	**.576 (.010)**	**.548 (.015)**	**.519 (.023)**	**.582 (.009)**
	Non-pers. Errors	**.464 (.045)**	**.518 (.023)**	.456 (.050)	**.469 (.043)**
	No. of complete categories	-.423 (.071)	**-.559 (.013)**	-.387 (.101)	.335 (.161)
	No. of cards to complete 1st category	.022 (.360)	.162 (.507)	.273 (.257)	.245 (.312)
Cognitive flexibility (continuation)	Failure to maintain criteria	.049 (.842)	.153 (.531)	.045 (.855)	.094 (.703)
	Learn Learn	.020 (.934)	-.091 (.711)	.168 (.491)	.011 (.966)
	STROOP Interference	.307 (.201)	.199 (.414)	.445 (.056)	.138 (.574)

Note. WAIS-III: Wechsler Adult Intelligence Scale (3rd edition); BADS: Behavioral Assessment of the Dysexecutive Syndrome; WCST: Wisconsin Card Sorting Test; TMT: Trail Making Test; RCFT: Rey Complex Figure Test; Stroop – The Stroop Color and Word Test; RAVLT: Rey Auditory Verbal Learning Test; Benton: Benton Visual Retention Test

Discussion

One of the main aims of this research was to examine the prevalence of PTSD symptoms at clinically significant levels. The prevalence of 35% found in the present study is slightly above the prevalence of PTSD symptoms reported in previous studies, with percentages ranging between 10% and 32% (Abbey, Thompson, Hickish, & Heathcote, 2015; Parikh et al., 2015; Elklit & Blum, 2011; Naidich & Motta, 2000). These differences may be associated with the use of different measures; in fact, most of the studies used other evaluation tools, such as the PCL-C (Posttraumatic Stress Disorder Checklist – Civilian Version) and semi-structured clinical interviews, to obtain percentages of PTSD symptoms. Very few studies used the IES-R. This may be because most studies attempt to assess the existence of a diagnosis of PTSD rather than the suffering associated with some traumatic event such as the present study, so it is understandable that the prevalence in this study is slightly higher maybe reflecting the sensibility of the instrument used for screening. In future studies, this finding should be explored, namely by analyzing the potential impact of PTSD diagnosis on cognitive functioning of cancer patients.

One of the major strengths of this study was the extensive evaluation of neurocognitive functioning of participants, involving different cognitive domains (attention, memory, processing speed, and executive functions). This allowed to deeply explore patients' needs and cognitive difficulties with impact in daily life and its relationship with PTSD symptoms, which is typically higher in women with breast cancer. The descriptive results concerning participants' cognitive functioning also showed that a considerable percentage of the sample presented deficits in attention (sustained and divided / alternating), memory (visual and verbal long term), processing speed, and functioning (inhibition and cognitive flexibility). These results are consistent with other studies (Ahles et al., 2001; Bender et al., 2006; Schagen et al., 1999; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004) showing that cancer patients tend to present worst cognitive functioning and deficits in executive functions, although in the present study, the prevalence of cognitive deficits is higher than in previous studies (Rubio et al., 2011; Schagen et al., 1999). These prevalence differences may be due, in large part, to the methodological diversity observed in the different studies that used different neuropsychological tests to evaluate cognitive domains. In addition, the differences found across studies in terms of types of cancer, stage of disease, type of neuropsychological assessment battery applied,

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DOI: 10.7714/CNPS/15.2.212

sample size, diagnosis time, etc. can interfere in the comparability of prevalence rates. For future investigations, studies should take into account these methodological and clinical aspects in order to deeply understand their associations with the occurrence and explanation of cognitive impairment in these patients.

Regarding to the associations between traumatic symptomatology and cognitive functioning, the results suggested that higher levels of PTSD symptoms seem to be associated with higher cognitive inflexibility and, more specifically, that higher levels of avoidance seem to be associated with impairments in processing speed. These results are according to previous studies that found an association between PTSD symptoms and processing speed and executive functions (Aupperle et al., 2012; LaGarde, Doyon, & Brunet, 2010). This is an important although exploratory finding, contributing to the growing evidence in the field since few are the studies that assessed PTSD symptoms in oncological patients in association with cognitive deficits. In fact, the studies that evaluated PTSD symptoms in association with cognitive deficits, were conducted mainly with war veterans' samples (Samuelson et al., 2006) and victims of child abuse (Bremner, Vermetten, Afzal, & Vythilingam, 2004). Future studies should deeply assess PTSD and/or traumatic symptomatology in patients with different types of cancer, since the features of this potential traumatic experience could be different, as well as in its relationships with cognitive functioning. Even though, an explanatory hypothesis for PTSD symptoms to be associated with cognitive deficits, namely in executive functions, is that the brain regions affected in PTSD are the same involved in executive processes. According to Heim and Nemeroff (2009), the brain regions that are most associated with the development of PTSD are the prefrontal cortex, the hippocampus, and the amygdala. In turn, the prefrontal cortex is responsible for executive functions. This leads us to hypothesize that PTSD symptoms, and executive functions, as they share the same cerebral region (prefrontal cortex), may be influencing each other and may explain the associations between these two processes. It would be important to conduct longitudinal studies with larger samples to better understand the causal associations among PTSD symptoms and cognitive deficits, namely exploring the underlying processes. It is possible that psychological distress associated with a particular traumatic situation (e.g., a cancer diagnosis and treatments) may prompt negative implications on the cognitive functioning of the patient by the allocation of cognitive resources that would be fundamental for the accomplishment of daily tasks. However, it is also plausible that the cognitive (dis)functioning prior to the occurrence of the oncological disease makes certain patients more vulnerable to the development of PTSD symptoms by the inflexible negative interpretation they give to the disease and associated events.

Despite the contribution of this innovative and exploratory study to the advancement of knowledge in the field, allowing to understand the relation between PTSD symptomatology and cognitive functioning of breast cancer patients regardless of oncological treatments implemented, some limitations should be pointed out. The small sample does not allow the generalization of the results and determines that our conclusions should be interpreted with caution and studies be implemented focusing the mapping of the interplay between mental health and cognitive functioning. The cross-sectional design does not also allow to understand the cognitive functioning prior the diagnosis of cancer and its relationship with PTSD symptomatology trajectories over the course of disease, as well as the inverse influence. So, the implementation of a longitudinal study it is needed to explore the direction of these multiple influences. Another important limitation was the use of self-report measures in the evaluation of PTSD symptoms, which may have contributed for the patients making more negative appraisals about their emotional state.

Conclusions

The present research contributes to increase the knowledge about cognitive functioning in breast cancer patients. Despite the exploratory nature of this study, results are consistent with previous evidence showing the increased risk of (breast) cancer patients to develop traumatic symptomatology, as well as cognitive impairment during disease. Moreover, our findings also suggest the contribution of traumatic symptomatology to the cognitive impairment observed in these patients, besides chemotherapy treatments implemented, highlighting the importance of assess changes in women's mental health, namely PTSD symptoms, since the diagnosis and treatments, given their potential association with cognitive deficits, to early screen and intervene in higher vulnerable patients. Considering its neuropsychological functioning, it seems that women with breast cancer treated with chemotherapy are a vulnerable group for developing cognitive deficits (mainly at the level of attention and executive functioning), highlighting the importance of neuropsychology within the context of psycho-oncology, and the need to assess cognitive functioning of these women through the cancer trajectory. Qualitative studies to explore and describe cognitive difficulties, their impact on daily life and the perception of women about the evolution of these difficulties over time (before, during and after disease recovery) and its relations with mental health status are, for this

ISSN: 0718-4123
DOI: 10.7714/CNPS/15.2.212

reason, needed. Finally, this study also provides important clues for future studies and for the development of interventions with this target audience, suggesting that it is important to identify risk factors for PTSD symptoms in patients with breast cancer and to develop specific psychological interventions targeting trauma and cognitive rehabilitation in order to promote cognitive flexibility.

Conflict of interest statement

There are no conflicts of interest to declare.

Ethical approval statement

The manuscript meets the guidelines for ethical conduct and report of research. The research project was approved by the institution (holistic center) where the research was implemented. Participants' informed consent was obtained.

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