

The Effects of Chemotherapy on the Contrast Sensitivity Function of Breast Cancer Patients

Natanael Antonio dos Santos (Corresponding author)

Department of Psychology

Universidade Federal da Paraíba

Cidade Universitária, João Pessoa, PB, Brasil

Tel: 55-83-3235-4439 E-mail: natanael_labv@yahoo.com.br / natanael.santos@pq.cnpq.br

Suellen Marinho Andrade

Department of Psychology

Universidade Federal da Paraíba

Cidade Universitária, João Pessoa, PB, Brasil

Haydee Casse da Silva

Department of Physiotherapy

Faculdade Ciências Médicas, Centro, João Pessoa, PB, Brasil

Received: August 16, 2011 Accepted: October 1, 2011 Published: December 1, 2011

doi:10.5539/ijps.v3n2p29 URL: <http://dx.doi.org/10.5539/ijps.v3n2p29>

This research is supported by CNPq (National Council for Scientific and Technological Development)

Abstract

The aim of this study was to determine the contrast sensitivity curves of sine-wave gratings with spatial frequencies of women diagnosed with breast cancer compared to healthy women. The contrast threshold was measured using a temporal two-alternative forced choice psychophysical method. The results showed that all of the participants in the experimental group displayed lower contrast sensitivity for all tested frequencies than those in the control group. The results suggest that the use of chemotherapy drugs can alter the visual perception of sinusoidal grade stimuli.

Keywords: Visual perception, Contrast sensitivity, Breast cancer, Chemotherapy

1. Introduction

The designation 'breast cancer' refers to the formation of a malignant tumor in the glandular structures and ducts of the breast (All-Hajj & Wicha, 2003). A malignant tumor in the breast is potentially curable when detected early. However, current recommendations for the treatment of breast cancer have been combinations of surgery, radiotherapy, and chemotherapy in the quest to eradicate the primary tumor and occult micro-metastases before the spread of cancerous cells (Schroen & Brenin, 2010).

Many side effects of chemotherapy, both short and long term, have been described in literature. However, although many women complain of subjective changes in memory and ability to think and see clearly during and after chemotherapy, the more subtle side effects have received little attention and are difficult to identify due to the lack of adequate measures (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000).

Currently, the contrast sensitivity function (CSF) has been widely used to assess and diagnose neuropathological changes in the visual sensory pathways and in the nervous system, produced by various diseases or disorders such as cancer (Grochowicki, Vighetto, Berquet, & Sassolas, 1990) and mercury intoxication (Ventura et al., 2005). The CSF is a practical and objective instrument used to study how diseases or other conditions interact with the nervous system and how this is reflected in the visual response (Santos, Alencar, & Dias, 2009).

Although the CSF has been employed as a method of evaluating the visual system in patients exposed to toxic substances (Fenske, Kissel, Shirai, Curl, & Galvin, 2004; Storm & Mazor, 2004), experiments related to the visual system's response to the effects of antineoplastic drugs in women with breast cancer, using CSF as a measuring tool, are still rare.

In this sense, the aim of the present study was to determine and compare the CSF between healthy women and those undergoing treatment for breast cancer. The general proposition was to verify whether the use of chemotherapy during cancer treatment would alter the sensory threshold curve or the visual perception of women with cancer. The measurements of threshold or contrast sensitivity to stimuli of sinusoidal-type grade, with average luminance of 40.1 cd/m², were taken with the psychophysical method of forced choice.

2. Material and Methods

2.1 Participants

Twenty women between the ages of 35 and 48 years participated in the study (Table 1), divided into two groups. The Experimental Group consisted of ten women who had completed a full course of adjuvant chemotherapy with the FAC system (5-fluorouracil [801 mg/day], adriamycin [80.1 mg], and cyclophosphamide [801 mg/day]), for at least 4 months from the start of the experiment, and showed no clinical evidence of the recurrence of local breast cancer or of metastases. The Control Group consisted of ten healthy female volunteers.

Table 2 presents the clinical regime related to the proportion of drugs administered to the patients in the Experimental Group.

The participants had no ocular diseases and had been examined by an ophthalmologist in the last 12 months. Both groups had normal or corrected visual acuity.

The participants in the Experimental Group were diagnosed at the early stages of breast cancer (stage I or II), but had no history of cancer or other serious diseases. The control group participants were diagnosed with the absence of associated pathologies. Other eligibility criteria for the groups were: female, between 30 and 50 years of age. Individuals with severe cognitive dysfunction (such as delirium, moderate to severe dementia, or aphasia), history of drug or alcohol abuse, psychiatric illness, and those taking psychoactive medications were excluded from the study.

The sample was selected from among the women patients hospitalized at the public hospital (Experimental Group) and from women who were their relatives or escorts (Control Group), recruited concurrently. The participation was conditioned to the signature of a free and informed consent according to Resolution n° 196/96 of the Brazilian National Health Council (Health Ministry, Brazil), which determines guidelines for research involving human beings in compliance with the Declaration of Helsinki. The local Ethics Committee approved this research.

2.2 Equipment and Visual Stimulus

The stimuli were generated and displayed at the center of a 21-inch, monochromatic, CRT Clinical Medical digital video monitor, in high resolution (1024 x 768), 70 Hz frame rate, with entry being controlled by a microcomputer through a VGA video card with DVI connectors. The luminance of the monitor was expanded from 8 to 14 bits with assistance of BITS++ (Cambridge Research Systems, Rochester, Kent, England, 2002), allowing for the use of visual stimuli with lower degrees of contrast. Light Scan software, equipped with an Optical Photometer (Cambridge Research Systems, Rochester, Kent, England, 2002), measured the luminance of the screen and performed the gamma correction of the monitor, using 48 values in the range of 0 to 255 (gamma = 1.8) as samples. The screen's lowest and highest luminance values were of 0.20 cd / m² and 80.0 luminance cd / m² (average of 40.1 cd / m²) and luminance around the stimulus was the lowest luminance (0.20 cd / m²). The room size was 2.5 x 2.0 m, illuminated by a 20W Philips® fluorescent lamp, and the walls of the room were gray-toned for better control of lighting conditions during the experiment. A computer program developed in the C++ language by the Perception, Neuroscience, and Behavior Laboratory (LPNeC), was used to perform the experiment (to generate and control the presentation of stimuli and to record the contrast thresholds).

The achromatic and vertical static sine-wave grating stimuli with spatial frequencies of 0.25, 1.0, 2.0 and 8.0 cycles per degree (cpd) of visual angle were used (Figure 1).

These stimuli were used to measure CSF, defined as:

$$L(x) = L_m [1 + c \sin(2\pi f x + \phi)]$$

where $L(x)$ is the luminance value at a point on the sinusoidal wave, L_m is the mean luminance, c is the contrast (Michelson's formula), f is the frequency in terms of cycles per degree, and ϕ is the spatial phase.

All stimuli had a diameter of approximately 7.2 degrees of visual angle and were designed to be displayed in the center of the screen at a viewing distance of 150 cm from the monitor. A fixed chair and a table with chin and forehead supports were used, in order to avoid changes in this viewing distance.

2.3 Procedures

The estimates were taken using the psychophysical method of forced choice between two temporal alternatives [6,9,10]. This method is based on calculating the probability of consecutive correct responses by the participant, in other words, in about 100 presentations of choices between two stimuli, the spatial frequency (test stimulus) is perceived 79% of the time by the volunteer. The procedure for measuring the threshold of each frequency consisted of a simple successive presentation of a pair of stimuli, with the participant having to choose among the two which one contained the spatial frequency. The other stimulus was always a homogeneous standard, with average luminance of 40.1 cd/m². The criterion adopted to vary the contrast of each spatial frequency tested was to make three consecutive correct responses to decrease by one unit and one wrong response to add (20%) to the same unit.

An experimental design with repeated measurements was used, in accordance with general practices in the research on visual perception using psychophysical methods. Studies of this nature involve a small number of volunteers in each condition or presentation of the other stimulus during 2s, followed by the volunteer's response.

During each experimental session a sequence of stimuli was presented, beginning with an audible tone, followed immediately by the presentation of the first stimulus for 2 seconds, then by a 1 second interval between stimuli, then the presentation of a second stimulus for 2 seconds, followed by the participant's response. The presentation order of the stimuli was randomized. If the response was correct, it was followed by another audible tone and then an interval of 3 seconds for the sequence to repeat. The audible tone indicating the start of the presentation of the pair of stimuli was different from the tone indicating a correct response.

The participants were instructed to press the left mouse button (labeled with the number 1) when the frequency was presented first and the right button (labeled with the number 2) when it was presented second, that is, after the neutral stimulus. Each session began with the test stimulus at a supra-threshold level of contrast and the experiments began only when the researcher was convinced that the participant had understood and responded according to the instructions.

The experimental session varied in time of duration (with an average time of 10 to 15 minutes) depending on the erroneous and correct responses made by the participant, until providing a total of six reversals (or six contrast values, three maximum and three minimum).

Each of the points (or frequencies) on the contrast sensitivity curve was estimated at least twice (two experimental sessions) on different days for each participant. On average, 20 curves were measured for each group of volunteers, totaling 80 experimental sessions. All of the estimates were performed with binocular vision and with no dilation or change of the pupil.

3. Results

After each session, the program produced a results sheet with the experimental status and the six contrast values obtained. The contrast values obtained for each frequency were grouped into spreadsheets and the large average used to estimate the contrast threshold (or contrast sensitivity) as a function of each spatial frequency tested.

Contrast sensitivity can be defined as the inverse of contrast threshold. Therefore, high threshold values are indicative of low sensitivities and vice versa.

The average threshold of the 12 contrast values obtained for each participant at each frequency was grouped into spreadsheets by state (with or without the use of chemotherapy), and the average values were used as an estimate of contrast sensitivity for each spatial frequency tested.

Figure 2 shows the contrast sensitivity curves (CSF) for both groups of women included in the study. The results showed that maximum sensitivity occurred in the frequency range of 1.0 cpd for women who used chemotherapy and for those in the control group.

The data also showed that women in the Experimental Group were 1.10; 1.26; 1.12; and 1.26 times more sensitive in detecting spatial frequencies of 0.25; 1.0; 4.0; and 8.0 cpd respectively, in comparison with those in the Control Group (Table 3). Thus, the results indicate that the CSF of women subjected to antineoplastic drugs was lower than that of healthy women for all spatial frequencies. In other words, the healthy women required less contrast to detect low, medium, and high spatial frequencies than those who used chemotherapy drugs.

The variance analysis (ANOVA) for repeated measurements showed a significant difference between the contrast thresholds of the Experimental Group and the Control Group, $F(2,27) = 80.09$; $p < 0.001$). The Bonferroni test was used for post hoc comparisons. The analysis showed significant differences between all frequencies ($p = 0.00$). The results show that the sensitivity to spatial frequencies is higher in healthy women than in women who used chemotherapy for the treatment of breast cancer (Table 4).

4. Discussion and Conclusions

The data from this study showed that the CSF is different between women who have had chemotherapy and healthy women. The use of drugs administered for the treatment of breast cancer causes a decrease in sensitivity at all frequencies; in other words, healthy women were 1.24 times more sensitive in detecting spatial frequencies of 0.25, 1.0, 4.0, and 8.0 cpd than women who had used the FAC system.

These results indicate that the CSF is different in both groups, implying that the performance of women with breast cancer in distinguishing objects from other objects in low contrast, can be alleviated by the use of chemotherapeutic medication, and that these drugs interact with the mechanisms that process low, medium, and high spatial frequencies.

This interaction can reduce the ability of patients to process global information on the shape of the stimulus – transmitted by low spatial frequencies, involving the magnocellular pathway – and details – transmitted by high spatial frequencies, involving the parvocellular pathway – considering that each frequency range conveys different types of information about an object (Santos, Oliveira, & Nogueira, 2009). In other words, the visual processing of shape and contrast involves at least two systems: the parvocellular visual pathway, which specializes in the processing of medium and high spatial frequencies or fine details, and operates at high or photopic levels of luminance, and the magnocellular visual pathway, which specializes in processing low spatial frequencies and operates at low or scotopic levels of luminance (França & Santos, 2008).

The biggest difference between the groups occurred at the 8.0 cpd frequency, where women in the control group were approximately 1.46 times more sensitive than those in the experimental group. The 8.0 cpd frequency is related to the processing of finer information or details during the recognition of objects. This frequency finds itself more accurate in the central area of the retina, where the sensory receptors are abundant and represented by topographic maps in cortical areas, the electrical impulses being conducted by neurons of the parvocellular pathway to the cerebral cortex (Baldo & Haddad, 2003; Schwartz, 2004).

The data from this study indicate that receptor cells in the retina or the parvo and magnocellular pathways can be altered in subjects with breast cancer, due to possible influences of drug combinations of 5-fluorouracil, adriamycin, and cyclophosphamide. The desired actions of these drugs, mainly their cytotoxic and immunomodulatory capabilities are achieved at the expense of severe side effects. These drugs are not selective and are toxic also to healthy tissue. Thus, their components can reach the central nervous system in a systemic manner, causing changes in nerve cells including the primary visual cortex (Gardner & Martins, 2000).

Several studies demonstrate that ocular toxicity is strongly associated with adjuvant chemotherapy treatment for breast cancer (Wickremasinghe et al., 2007; Tager et al., 2010). Gianni et al. (2007) claim that ocular toxicity induced by chemotherapy is quite common and not easy to prevent. According to the authors, modern treatment regimes such as those involving cyclophosphamide, methotrexate, and combinations of 5-fluorouracil, may have considerable side effects on the visual system, reported in 18-42% of patients.

Eisner and Austin (2004) conducted a study to determine whether standard doses of antineoplastic drugs would affect visual sensations mediated by small wavelengths. To do this, they measured two types of visual fields (30-20 and 24-20) in women under daily treatment for breast cancer, using short wavelength automated perimeter (SWAP) and the psychophysical test of frequency doubling perimeter, observing the wavelength via cones (SWS). The results of this study indicated that use of adjuvant substances for the treatment of breast cancer affects some types of preferred visual pathways, especially SWS, affecting neural functions of the visual system.

The understanding of the effects of chemotherapy on information processing and brain physiology is still limited, and the visual system is a possible model for addressing this issue. Therefore, deepening the knowledge on how sensitivity to elementary stimuli could be affected by these drugs might enlighten this question. The results presented here suggest further researching on how different cortical areas involved in spatial vision might be adversely affected by these clinical conditions.

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Table 1. Age distribution of participants

Participants	Age
Control Group	
1	35
2	41
3	37
4	44
5	48
6	37
7	39
8	42
9	45
10	41
Experimental Group	
11	46
12	40
13	42
14	39
15	41
16	36
17	48
18	36
19	42
20	43

Table 2. Proportion of antineoplastic chemical components administered

Experimental Group (n=10)	Chemical Components		
Participants	5-fluorouracil	Adriamycin	Cyclophosphamide
1	775 mg	77.5 mg	775 mg
2	850 mg	85 mg	850 mg
3	850 mg	85 mg	850 mg
4	755 mg	75.5 mg	755 mg
5	775 mg	77.5 mg	775 mg
6	775 mg	77.5 mg	775 mg
7	850 mg	85 mg	850 mg
8	775 mg	77.5 mg	775 mg
9	850 mg	85 mg	850 mg
10	755 mg	75.5 mg	755 mg
Mean	801 mg	80.1 mg	801 mg

Table 3. Average values (standard error) of contrast thresholds for 0.25, 1.0, 4.0, and 8.0 cpd in each condition (Experimental Group and Control) and the ratio between the mean values of groups

SC/Frequency	0.25	1.0	4.0	8.0
Control Group	65.18 (2.3)	162.95 (6.4)	53.43 (2.2)	12.49 (1.6)
Experimental Group	58.97 (1.7)	128.80 (4.9)	47.90 (2.5)	8.56 (0.9)
Ratio	1.10	1.26	1.12	1.46

Table 4. Multiple comparisons between frequencies of 0.25, 1.0, 4.0, and 8.0 cpd.

Frequencies		Mean Difference	Std. Error	Sig. a	95% Confidence Interval for Difference a	
					Lower Bound	Upper Bound
0.25	1.0	-83.813*	12.978	.000	-122.018	-45.608
	4.0	11.395*	6.409	.000	-7.472	30.262
	8.0	51.535*	4.382	.000	38.633	64.436
1.0	0.25	83.813*	12.978	.000	45.608	122.018
	4.0	95.208*	10.268	.000	64.981	125.435
	8.0	135.348*	11.596	.000	101.211	169.484
4.0	0.25	-11.395*	6.409	.000	-30.262	7.472
	1.0	-95.208*	10.268	.000	-125.435	-64.981
	8.0	40.140*	3.989	.000	28.398	51.882
8.0	0.25	-51.535*	4.382	.000	-64.436	-38.633
	1.0	-135.348*	11.596	.000	-169.484	-101.211
	4.0	-40.140*	3.989	.000	-51.882	-28.398

* The mean difference is significant at the 0.05 level.

Adjustment for multiple comparisons: Bonferroni

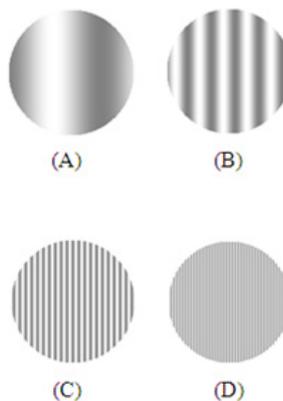


Figure 1. Standard sinusoidal grating stimuli with spatial frequencies of: (A) 0.25 cpd; (B) 1.0 cpd; (C) 4.0 cpd; (D) 8.0 cpd; and (E) the visual stimulus at mean homogeneous luminance. All stimuli represented as originally calibrated for a 150 viewing distance

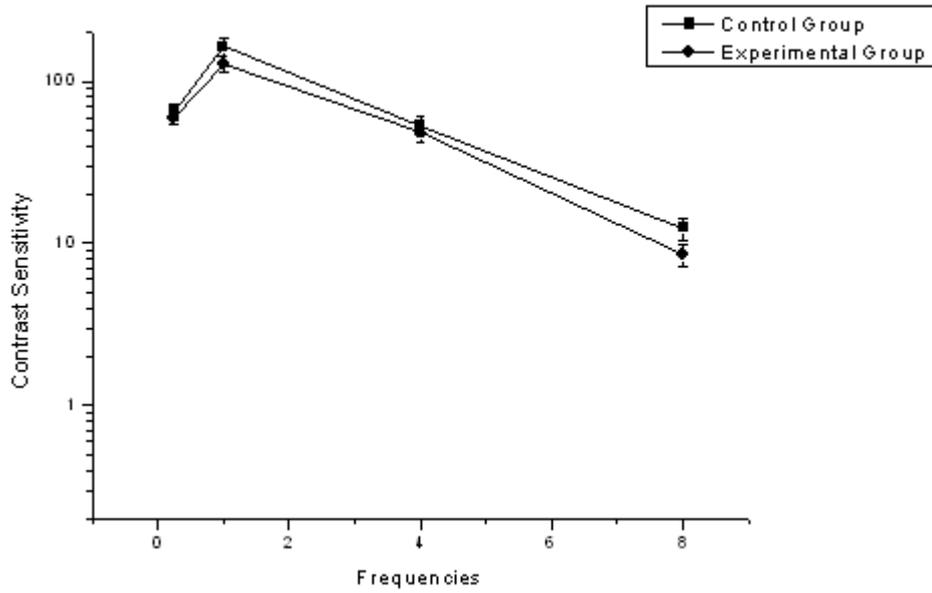


Figure 2. Contrast sensitivity curves for spatial frequencies among healthy control women (—■—) and those subjected to chemotherapy (—●—). The vertical lines show the average standard error for each spatial frequency (0.25, 1.0, 4.0, and 8.0 cpd)