Brief Report

Cognitive Impairment in a Subset of Breast Cancer Patients After Systemic Therapy—Results From a Longitudinal Study

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Abstract

Context. Studies indicate adverse effects of breast cancer (BC) and cancer treatment on cognitive function.

Objectives. To investigate the effects of systemic treatment on cognitive performance in BC patients.

Methods. Participants were BC patients scheduled to receive systemic treatment (BC + SYST; $n = 31$), or no systemic treatment (BC; $n = 24$) and no-cancer (NC) controls ($n = 33$). Neuropsychological examinations were used to study cognitive performance on 18 tests grouped into eight cognitive domains, before adjuvant treatment (T1) and six months after chemotherapy (T2), or at similar intervals. We also assessed health-related quality of life, anxiety and depression, mood, stress, and cognitive problems. Analysis of variance was used to assess group differences of cognitive performance and multivariate normative comparison to classify impairment, comparing scores of each participant against the distribution of the scores of NC controls.

Results. Of BC + SYST, 16% were cognitively impaired at T2, compared to 4% in BC and 6% in NC. Although not significant, we observed moderate effect sizes for worse performance in the BC + SYST group compared to NC (Flanker congruent [effect size {ES} = 0.44] and stimulus incongruent [ES = 0.44]) and compared to BC (Controlled Oral Word Association Test [ES = 0.47], digit span [ES = 0.41], and Hopkins Verbal Learning Test immediate [ES = 0.71] and delayed recall [ES = 0.65]). Cognitively impaired patients had a significantly lower estimated premorbid intelligence, worse physical and social functioning, and more distress at T2 compared to unimpaired patients.

Conclusion. Our findings indicate that cognitive impairment after systemic treatment occurs in a subset of BC patients. The predictive value of demographic and psychosocial factors in cognitive impairment should be further investigated in a larger sample of impaired patients. J Pain Symptom Manage 2016;52:560–569 © *2016 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Breast cancer, chemotherapy, cognitive impairment, adverse effects, longitudinal study

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Introduction

A large number of studies have investigated cognitive performance after cancer treatment, mainly focusing on chemotherapy. Although the prevalence and severity of impairment varies, most studies show that cancer treatment–related cognitive impairment (CRCI) occurs after chemotherapy.[1] Imaging studies have documented structural injury to the brain and alterations in regional brain activity.[2] Animal models have identified mechanisms by which these adverse effects on brain structure and function may impact cognition, including toxic effects on neural progenitor cell populations.[3] Several studies have pointed to potential risk factors for developing CRCI such as higher chemotherapy dose,[4,5] cytostatic agent,[6] lower cognitive reserve,[7] and genetic factors.[8,9]

Recently, CRCI has also been reported before chemotherapy[10,11] and in cancer patients who did not receive chemotherapy.[12] Our own research has shown that cognitive problems before systemic treatment co-occurred with differences in brain activation and structure.[13] These differences, which were independent of staging, appeared to be driven by fatigue, although other studies have found other psychosocial and biological factors contributing to pretreatment cognitive problems.[14–18] These factors, including surgical and genetic factors, may also add to the development of CRCI in cancer patients, stressing the importance of a baseline assessment when evaluating the impact of chemotherapy on cognition.

In line with recommendations by the International Cognition and Cancer Task Force (ICCTF),[19] most current reports of CRCI are prospective, taking into account cognitive performance before treatment. A consistent pattern of cognitive decline was reported in 19 of 22 prospective studies.[1] However, incidence rates and severity of these impairments vary between studies. This discrepancy may be attributable to differences in the reference groups against which cognitive performance in patients is compared (i.e., breast cancer [BC] patients not being treated with chemotherapy, healthy controls, and/or published normative data).[1] In addition, the different ways in establishing cognitive impairment add to these discrepancies, for example, group-level comparisons based on either test or domain scores, and classification of individual performance based on different multivariate methods (reliable change index and standardized regression based models). However, these outcomes are based on cutoff scores and highly depend on the chosen threshold above which a person is categorized as being cognitively impaired.[20]

In this prospective study, we systematically investigated CRCI in BC patients by 1) comparing BC patients receiving systemic treatment (BC + SYST) to women without cancer, and controlling for potential other cancer-related aspects by adding a group of BC patients not requiring systemic treatment (BC) and 2) studying cognitive performance at the group level by comparing test performance between groups, as well as applying a multivariate method to identify individual patients demonstrating a deviating pattern of cognitive performance.

Methods

Subjects

Participants were patients with BC, either scheduled to receive adjuvant anthracycline-based chemotherapy with or without endocrine treatment (BC + SYST), or who did not require systemic treatment (BC) and age-matched no-cancer (NC) controls. BC patients were recruited through their treatment team at the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, VU University Medical Center, Flevoziekenhuis, Reinier de Graaf Gasthuis, and Academic Medical Center Amsterdam. Subjects were eligible if they met the following criteria: female, less the age of 70 years, sufficient command of the Dutch language, no previous malignancies. In addition, patients had to have a diagnosis of primary breast cancer, no distant metastases, and no other treatment than surgery at the time of baseline assessment. Patients with recurring tumors at the follow-up assessment were excluded. Patients scheduled to receive trastuzumab were not eligible because the effects of immunotherapy on cognition are unknown and because of the longer treatment duration compared to other therapies. NC controls were recruited via participants, as well as through advertisements in the participating hospitals.

The study was approved by the institutional review board of The Netherlands Cancer Institute, serving as the central ethical committee for all participating institutes. Written informed consent was obtained according to the declaration of Helsinki and following institutional guidelines. The experiment was conducted at the Academic Medical Center of the University of Amsterdam and the Spinoza Center for Neuroimaging.

Procedures

Baseline data were collected after surgery, before the start of adjuvant treatment (T1). Follow-up assessments took place at approximately six months after chemotherapy for the BC + SYST group and at matched intervals for the BC and the NC groups (T2).

The assessment consisted of seven questionnaires to assess health-related quality of life, anxiety and

depression, mood, stress, cognitive problems, and personality dimensions (Supplementary Table 1). In addition, the Impact of Events Scale was used to assess distress related to breast cancer at T2.[21] A comprehensive neuropsychological test battery was used, consisting of 18 test indices, grouped into the domains of executive function, attention, visual memory, verbal memory, processing speed, and motor speed (Supplementary Table 1). Selection of tests was based on recommendations by the ICCTF as well as previous studies and has been previously described in detail in Menning et al.[13] Multimodal MRI was acquired, analyses of which will be described elsewhere.

Statistical Analysis

Descriptive statistics were used to characterize the study sample.

Raw neuropsychological test scores were converted to standardized z-scores based on the mean and SD of baseline performance of the NC group. Differences in patient-reported outcomes (PROs) at T2, adjusted for T1, were analyzed using univariate analysis of covariance.

To assess cognitive performance, two methods were applied: 1) differences at the group level at T2, adjusted for T1, were assessed using analysis of covariance. Age and IQ were additionally added as covariates. The *P*-value for overall model effects and specific contrasts was set at 0.05, lowering the risk of Type I errors due to multiple testing. Differences in mean scores were accompanied by effect sizes (ESs). Standardized effect sizes were calculated by dividing the difference in mean scores between the groups by the pooled SD. Effect sizes of 0.2 were considered small, 0.5 moderate, and 0.8 large,[22] 2) To identify cognitively impaired subjects, multivariate normative comparison (MNC) was applied, which is a method adequate for small sample sizes.[23] MNC compares an individual's test scores against the distribution of the same scores in the control sample. The false-positive rate is controlled by performing only one comparison. The critical alpha value was set at 0.05 one-sided, in accordance with Huizenga et al.[23] MNC calculations were based on T2 performance residual scores, that is, the difference between an individual's score and her predicted score based on baseline performance, age, and IQ. Predicted scores were calculated using regression coefficients that were estimated in the NC group.

In addition, we looked for confounding effects of PROs in the group analyses of neuropsychological performance. PROs were included in the analyses when 1) a strong relation was expected based on literature (fatigue, health-related quality of life, anxiety and depression, perceived stress, overall mood, cognitive complaints, and distress), and/or 2) significant group differences were found. Because estrogen exposure and pretreatment menopausal status have been linked to cognitive performance,[24,25] we also investigated the effects of these factors. All analyses were performed using SPSS 22 (IBM, Armonk, NY), except for the MNC analyses which were performed using a web site dedicated to this purpose (http://purl.oclc.org/NET/RGRASMAN/MNC).

Results

At T1, before the start of adjuvant treatment, 32 BC + SYST, 33 BC and 38 NC controls were included (see Menning et al.[13] for recruitment details). At T2, five NC controls dropped out because of personal reasons including "illness in the family" and "no time." One patient in the BC + SYST group declined to undergo the neuropsychological assessment due to performance anxiety. We originally wanted to examine the contribution of endocrine therapy on cognition. Because of the unexpected large imbalance in hormonal treatment between and within the two breast cancer groups (BC + SYST, 71%; BC, 27%), this was not possible. Therefore, we excluded nine patients receiving hormonal treatment from the BC group to create a group not receiving any systemic treatment.

No significant differences in demographic variables or neuropsychological performance at T1 between participants and decliners were found. Final analyses were performed with 31 BC + SYST, 24 BCs, and 33 NC controls (see Fig. 1).

Subject Characteristics

Subject characteristics are presented in Table 1. No significant differences in age, premorbid IQ, or level of education were found. A marginally significant group difference in time between T1 and T2 was found. Including this factor as a covariate in further analyses did not change the outcomes. At T1, 39% BC + SYST, 54% BC, and 55% NC subjects were postmenopausal. In the BC + SYST group, all premenopausal women became postmenopausal after treatment.

We found significant overall differences between groups at T2 in physical and social functioning, fatigue (Quality of Life Questionnaire Core 30 [QLQ-C30]) and cognitive complaints (Table 2). Post hoc analyses demonstrated lower physical ($P = 0.006$) and social functioning ($P = 0.007$), more fatigue ($P = 0.001$), and more cognitive complaints ($P = 0.006$) at T2 in BC + SYST compared to NC and more cognitive complaints for BC + SYST vs. BC ($P = 0.003$).

Neuropsychological Performance

Neuropsychological test scores at T2 did not significantly differ between groups (Table 3). However, we

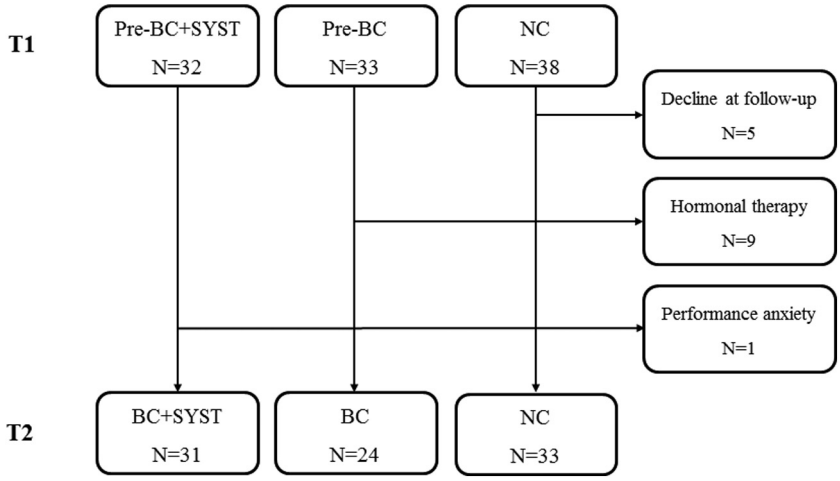

Fig. 1. Flow diagram of subject accrual. T1 = after surgery and before adjuvant treatment; T2 = six months after the last chemotherapy cycle, or at matched intervals; pre-BC + SYST = breast cancer patients before systemic treatment; pre-BC = breast cancer patients not scheduled to undergo systemic treatment; NC = no-cancer; BC + SYST = breast cancer patients receiving systemic treatment; BC = breast cancer patients not requiring systemic treatment.

did find small-to-moderate effect sizes for the Flanker congruent trials (ES = 0.44) and Flanker stimulus incongruent trials (ES = 0.44) between BC + SYST and NC (Table 3). Comparing BC + SYST to BC, we found small to large effects for Controlled Oral Word Association Test (ES = 0.47), Digit Span

Table 1
Subject and Treatment Characteristics

Variable	BC + SYST (n = 31)	BC (n = 24)	NC (n = 33)	P
Age at T1 (yrs)	49.8 (9.16)	51.2 (6.80)	51.4 (8.3)	0.712
Estimated IQ (NART)	102.2 (13.5)	104.0 (13.3)	107.4 (11.8)	0.255
Education level [n (%)]				NA
Low	0 (0)	0 (0)	0 (0)	
Middle	4 (13)	3 (13)	0 (0)	
High	27 (87)	21 (87)	33 (100)	
Interval T1–T2 (days)	331 (71)	341 (32)	366 (61)	0.052
Postmenopausal [n (%)]				
T1	12 (39)	13 (54)	18 (55)	0.372
T2	31 (100)	14 (58)	18 (55)	<0.001
Lifetime estrogen exposure (yrs)	32.1 (5.9)	34.0 (5.9)	33.3 (6.0)	0.476
Medication use at T2 [n (%)]				NA
Antidiabetic	0 (0)	1 (4)	1 (3)	
Cardiovascular	5 (16)	5 (21)	8 (24)	
Psychotropic	7 (23)	1 (4)	3 (9)	
Breast cancer stage [n (%)]				NA
0	0	13 (54)		
1	19 (61)	11 (46)		
2	11 (36)	0		
3	1 (3)	0		
Treatment [n (%)]				
Surgery [n (%)]				0.681
WLE	19 (61)	16 (67)		
Ablatio	12 (39)	8 (33)		
Radiotherapy	25 (81)	16 (67)		
Tamoxifen	22 (71)	NA		
Chemotherapy regimen [n (%)]				
AC[a]	3 (10)			
AC–docetaxel[b]	21 (68)			
AC–paclitaxel[c]	3 (10)			
FEC[d]	4 (13)			
Days since chemotherapy	207 (72)			

BC + SYST = breast cancer patients receiving systemic treatment; BC = breast cancer patients not requiring systemic treatment; IQ = estimated premorbid intelligence; NC = no-cancer; NART = Dutch version of the National Adult Reading Test; WLE = wide local excision; AC = doxorubicin (Adriamycin), cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide.
Values indicate mean ± SD unless indicated otherwise.
[a]Four or six cycles.
[b]Three or six cycles.
[c]Four cycles AC followed by four or 12 cycles of paclitaxel.
[d]Three or six cycles. Differences are considered statistically significant at a critical alpha value of 0.01.

Table 2
Patient-Reported Outcomes

Variable	T1			T2			*P*
	BC + SYST ($n = 31$)	BC ($n = 24$)	NC ($n = 33$)	BC + SYST ($n = 31$)	BC ($n = 24$)	NC ($n = 33$)	
QLQ-C30							
Physical functioning[§]	91.8 (11.5)	87.9 (12.14)	96.88 (7.37)	84.5 (16.6)[a]	88.6 (16.6)	97.1 (6.3)	0.008
Social functioning[§]	79.6 (23.1)	77.8 (26.3)	100 (0)	78.0 (21.7)[a]	88.9 (20.7)	89.8 (11.7)	0.004
Cognitive functioning[§]	81.2 (24.2)	80.6 (28.1)	92.7 (12.7)	73.1 (23.0)	82.6 (17.4)	89.6 (25.3)	0.075
Emotional functioning[§]	74.2 (22.8)	82.6 (18.9)	89.8 (12.8)	83.3 (18.8)	84.4 (15.4)	91.1 (12.1)	0.537
Global quality of life[¶]	76.1 (17.8)	74.7 (16.2)	89.3 (10.0)	74.2 (15.9)	80.6 (23.1)	89.8 (11.7)	0.081
Fatigue[#]	24.0 (23.5)	35.2 (26.8)	11.81 (16.2)	30.5 (25.2)[a]	19.4 (22.3)	12.5 (14.6)	0.001
HSCL-25	13.7 (13.9)	11.2 (11.6)	6.2 (7.7)	11.7 (13.0)	8.9 (9.2)	4.2 (4.9)	0.120
PSS	24.4 (6.7)	19.9 (8.3)	18.7 (5.0)	21.7 (6.9)	19.8 (5.9)	18.3 (4.9)	0.826
POMS							
Total score	17.5 (16.0)	15.5 (13.0)	9.0 (4.9)	14.0 (9.9)	9.6 (5.2)	9.3 (6.2)	0.099
Fatigue subscale	2.5 (4.0)	3.5 (5.4)	1.1 (1.5)	2.3 (2.9)	1.9 (2.4)	0.8 (1.5)	0.112
MOS-cog	81.2 (16.7)	72.9 (17.6)	84.6 (11.5)	73.3 (18.6)[a]	79.8 (13.0)	85.2 (10.3)	0.001
IES	NA	NA	NA	26.4 (11.1)	21.9 (11.6)	NA	0.062

BC + SYST = breast cancer patients receiving systemic treatment; BC = breast cancer patients not requiring systemic treatment; NC = no-cancer; QLQ-C30 = European Organization for Research and Treatment of Cancer Health-Related Quality-of-Life Questionnaire: scores range from 0 to 100, higher score indicates [§]better functioning, [¶]better quality of life, or [#]more symptoms; HSCL-25 = Hopkins Symptom Checklist−25: scores range from 0 to 100, higher score indicates higher levels of anxiety and depression; PSS = Perceived Stress Scale: scores range from 10 to 50, higher scores indicate higher levels of perceived stress; POMS = Profile of Mood States, higher scores indicate more problems; MOS-cog = Cognitive Functioning Scale of the Medical Outcomes Study, lower scores indicate more problems; IES = Impact of Event Scale, higher scores indicate more distress.
Values indicate mean ± SD unless indicated otherwise.
P-values indicate overall group differences at T2 adjusted for scores at T1.
[a]Indicates a significant difference with NC at $P < 0.01$.

(ES = 0.41), and Hopkins Verbal Learning Test immediate (ES = 0.71) and delayed recall (ES = 0.65) (Table 3). These results indicate worse performance in the BC + SYST group compared to BC and NC.

Including patient-reported outcomes as an additional covariate in the group analyses did not change the results. In addition, no association between neuropsychological test scores and estrogen exposure or menopausal status was found.

Using multivariate normative comparisons, five BC + SYST patients (16%) were identified as cognitively impaired at T2. One patient (4%) in the BC group and two (6%) NC controls showed a negatively deviating pattern of test scores, as expected under the null distribution. Chi-square test showed no significant difference in the proportion impaired subjects between groups ($P = 0.231$).

Secondary Analyses

Characteristics of BC patients classified as being impaired and unimpaired at T2 are summarized in Table 4. Impaired patients had lower IQs than unimpaired patients ($P = 0.005$). We found that impaired patients showed worse physical ($P = 0.002$) and social functioning ($P = 0.004$), and more symptoms of anxiety and depression ($P = 0.008$) at T2, compared to unimpaired patients.

Although not significant at our a priori threshold ($\alpha = 0.01$), impaired patients showed higher levels of fatigue (QLQ-C30, $P = 0.062$, and Profile of Mood States, $P = 0.020$), higher levels of distress ($P = 0.019$), and lower quality of life ($P = 0.056$) at T2, compared to unimpaired patients.

Discussion

Using MNC, 16% of BC + SYST patients were classified as cognitively impaired at T2, compared to 4% in the BC and 6% in the NC group (as expected under the null distribution). Group comparisons of the neuropsychological test indices at T2 did not show significant differences. However, we did find moderate-to-large effect sizes indicating worse cognitive performance on a number of tests in the BC + SYST group after treatment.

Before treatment, we found that the observed worse cognitive performance, prefrontal hyperactivation, and lower white matter integrity of the BC patients compared to controls were related to fatigue, and not to, for example, differences in cancer staging.[13] Other studies have also suggested that psychosocial factors, such as worry,[14] fatigue,[15] and stress[18] may be linked to CRCI, before and after treatment. However, results on the predictability of these factors are inconsistent. We also could not identify a psychosocial factor that was related to cognitive performance after treatment; BC patients receiving systemic therapy did report more problems in cognitive, physical, and social functioning and fatigue, but these symptoms were not related to cognitive test performance. Interestingly, we did find prominent differences in several PROs between patients classified as impaired and

Table 3
Standardized Neuropsychological Test Performance

	Unadjusted Scores					Adjusted Scores			
	T1		T2						
Domain	M	SD	M	SD	*P*	Mean Difference	SDp	ES	CI
Executive function									
COWAT					0.318				
BC + SYST	−0.41	1.15	−0.70	1.25					
BC	0.02	1.13	−0.10	.86		0.282	.60	0.47	−0.08, 1.00
NC	0.00	1.00	−0.23	.75		0.163	.60	0.27	−0.22, 0.76
BADS Zoo test					0.625				
BC + SYST	0.10	1.13	0.10	.85					
BC	0.29	.94	0.33	1.12		0.174	.94	0.18	−0.35, 0.72
NC	0.00	1.00	0.26	.91		0.116	.94	0.12	−0.37, 0.61
TMT-B					0.296				
BC + SYST	−0.42	1.26	−0.14	1.70					
BC	−0.51	1.48	0.19	.97		0.394	1.01	0.39	−0.15, 0.92
NC	0.00	1.00	0.39	.90		0.303	1.01	0.30	−0.20, 0.79
Attention									
Flanker congruent					0.503				
BC + SYST	−0.20	1.15	−0.01	1.07					
BC	−0.30	1.18	−0.06	.99		0.072	.69	0.10	−0.43, 0.64
NC	0.00	1.00	0.41	1.41		0.303	.69	0.44	−0.07, 0.93
Flanker stimulus incongruent					0.522				
BC + SYST	−0.16	1.02	−0.16	.95					
BC	−0.26	1.05	−0.07	.88		0.18	.68	0.26	−0.28, 0.79
NC	0.00	1.00	0.25	1.22		0.301	.69	0.44	−0.06, 0.93
Flanker response incongruent					0.576				
BC + SYST	−0.07	.97	0.07	.90					
BC	−0.26	1.08	−0.08	.89		0.108	.67	0.03	−0.51, 0.56
NC	0.00	1.00	0.16	1.19		0.103	.67	0.16	−0.34, 0.64
VRT dominant hand					0.027				
BC + SYST	−0.48	1.19	−0.30	1.09					
BC	0.03	.67	−0.32	.95		−0.296	.85	−0.35	−0.88, 0.19
NC	0.00	1.00	0.06	1.10		0.119	.86	0.14	−0.35, 0.63
VRT nondominant hand					0.155				
BC + SYST	−0.39	.94	−0.56	1.31					
BC	−0.13	.58	−0.46	.86		−0.039	.86	−0.04	−0.58, 0.49
NC	0.00	1.00	−0.13	.95		0.216	.87	0.25	−0.25, 0.74
Digit span					0.677				
BC + SYST	−0.17	.95	−0.20	1.01					
BC	0.11	1.34	0.30	1.06		0.316	.77	0.41	−0.13, 0.94
NC	0.00	1.00	−0.07	1.10		−0.002	.77	0.00	−0.49, 0.49
Visual memory									
WMS immediate recall					0.258				
BC + SYST	−0.39	.65	0.06	.84					
BC	−0.33	1.01	−0.13	.96		−0.194	.77	−0.25	−0.78, 0.29
NC	0.00	1.00	0.20	.86		−0.017	.77	−0.02	−0.51, 0.47
WMS delayed recall					0.963				
BC + SYST	−0.04	.78	0.40	.76					
BC	−0.09	.83	0.38	.79		0.016	.71	0.02	−0.51, 0.56
NC	0.00	1.00	0.28	.79		−0.116	.71	−0.16	−0.65, 0.33
Verbal memory									
HVLT immediate recall					0.138				
BC + SYST	0.23	1.34	−0.19	1.29					
BC	0.46	.96	0.56	1.29		0.633	.90	0.71	0.15, 1.24
NC	0.00	1.00	−0.16	.98		0.205	.90	0.23	−0.27, 0.72
HVLT delayed recall					0.603				
BC + SYST	0.04	1.04	−0.13	1.22					
BC	0.18	.97	0.51	.77		0.565	.87	0.65	0.09, 1.19
NC	0.00	1.00	−0.19	1.18		−0.029	.88	−0.03	−0.52, 0.46
HVLT delayed recognition					0.452				
BC + SYST	0.20	.58	−0.11	.93					
BC	−0.02	.86	0.13	.90		0.317	.93	0.34	−0.20, 0.87
NC	0.00	1.00	−0.23	1.14		−0.117	.93	−0.13	−0.61, 0.37
Processing speed									
TMT-A					0.398				
BC + SYST	−0.32	1.20	−0.14	1.08					
BC	−0.14	1.06	0.19	.78		0.315	.91	0.34	−0.20, 0.88
NC	0.00	1.00	0.16	1.13		0.265	.92	0.29	−0.21, 0.78

(*Continued*)

Table 3
Continued

Domain	Unadjusted Scores					Adjusted Scores			
	T1		T2						
	M	SD	M	SD	*P*	Mean Difference	SDp	ES	CI
Digit symbol					0.101				
BC + SYST	−0.46	1.06	−0.43	1.14					
BC	−0.51	1.02	−0.43	1.03		0.047	.65	0.07	−0.46, 0.61
NC	0.00	1.00	−0.15	1.04		−0.083	.66	−0.13	−0.62, 0.37
Motor speed									
Tapping dominant hand					0.326				
BC + SYST	0.05	1.11	0.22	1.18					
BC	−0.35	.94	−0.20	.69		−0.115	.61	−0.19	−0.72, 0.35
NC	0.00	1.00	0.04	.88		−0.097	.60	−0.16	−0.65, 0.33
Tapping nondominant hand					0.163				
BC + SYST	−0.02	.99	0.13	1.24					
BC	−0.45	.72	−0.20	.62		0.081	.60	0.14	−0.40, 0.67
NC	0.00	1.00	−0.05	1.02		−0.117	.60	−0.19	−0.68, 0.30

M = unadjusted mean; SD = unadjusted standard deviation; SDp = pooled standard deviation of BC + SYST and BC or NC; ES = effect size of the post hoc analysis vs. BC + SYST; CI = confidence interval of the post hoc analysis vs. the BC + SYST group; COWAT = Controlled Oral Word Association Test; BC + SYST = breast cancer patients receiving systemic treatment; BC = breast cancer patients not requiring systemic treatment; NC = no-cancer; BADS = Behavioral Assessment of the Dysexecutive Syndrome; TMT = Trail Making Test; VRT = Visual Reaction Time Test; WMS-R = Wechsler Memory Scale—Revised; HVLT-R = Hopkins Verbal Learning Test—Revised.
P-values indicate overall group differences at T2 adjusted for scores at T1. Differences are considered statistically significant at a critical alpha value of 0.01. Mean difference, adjusted mean difference vs. the BC + SYST group.
Scores are standardized z-scores based on T1 scores in the NC group.

unimpaired. However, given the small number of impaired patients, this should be further investigated.

Previous studies usually describe cognitive impairment in a subset of patients,[12,26–28] with decline in up to 65% of BC patients after chemotherapy,[29–31] whereas we only observed cognitive impairment in 16% of BC + SYST patients. A possible explanation for this difference is an association between age and IQ and CRCI. Several studies have shown that older patients[7,32,33] and patients with lower cognitive performance or lower level of education before treatment[7,32] are more vulnerable to the development of CRCI. The current sample consisted of relatively young and highly educated women, who may be able to maintain performance due to a higher cognitive reserve.[7] This hypothesis is further supported by our finding of lower estimated IQ in cognitively impaired vs. unimpaired patients. Still, higher frequencies of CRCI have also been reported in patients with similar demographic characteristics and similar treatment regimens to those in this study.[30,31,34]

Other reasons for the different outcomes in our study compared to previous research could be that the definition of cognitive dysfunction is variable between studies, ranging from a small number of domain scores to over 20 test indices,[5,30,35–37] with no consistent number of abnormal test or domain scores required to classify cognitive impairment. We included all cognitive tests recommended by the ICCTF[19] and added several validated and commonly used neuropsychological tests, to cover all cognitive domains. Moreover, we used MNC, which compares an individual's complete cognitive test battery against the norm group, thereby eliminating the multiple comparison problem.[23] MNC detects subtle differences in cognitive impairment as it is sensitive to deviations in the cognitive profile,[23] which has been shown to be a significant predictor for daily functioning.[38] Most studies do not correct for the number of tests included in the study, thereby possibly overestimating the frequency of CRCI.

Strengths of this study are the longitudinal design, the low attrition rate, and the use of MNC to identify subjects with negatively deviating patterns. Another strength is the inclusion of two control groups: BC and NC. Although differences in neuropsychological test performance did not reach significance at the group level, both patient groups seemed to perform worse on a number of tests both before and after treatment compared to NC. BC patients who did not require systemic treatment appeared to show larger recovery in cognitive performance compared to BC patients who had received systemic treatment. By excluding the BC patients receiving endocrine treatment in the absence of chemotherapy, we can conclude that the differences found between the two patient groups are linked to systemic treatment. However, we were not able to disentangle the effects of chemotherapy and endocrine treatment. In addition, all women who had received systemic treatment became postmenopausal. In some studies, menopausal status has been linked to cognitive decline;[25,39] however, in this study, no relation between cognition and pretreatment menopausal status was found,

Table 4
Characteristics of Impaired and Unimpaired Patients

Variable	Impaired ($n = 6$)	Unimpaired ($n = 49$)	P
Age at T1 (yrs)	53.6 (4.9)	50.0 (8.4)	0.323
Estimated IQ (NART)	89.0 (14.8)	104.7 (12.2)	0.005
Education [n (%)]			
Low	0 (0)	0 (0)	NA
Middle	3 (50)	4 (8)	
High	3 (50)	45 (92)	
Interval T1–T2	328.5 (217–461)	336.3 (196–460)	0.756
Treatment [n (%)]			
Radiotherapy	6 (100)	35 (71)	0.129
Endocrine therapy	4 (67)	18 (37)	0.158
Chemotherapy	5 (83)	26 (53)	0.158
Chemotherapy regimen			
AC[a]	0 (0)	3 (6)	NA
AC–docetaxel[b]	4 (67)	17 (35)	
AC–paclitaxel[c]	0 (0)	3 (6)	
FEC[d]	1 (17)	3 (6)	

	T1		T2		
	Impaired	Unimpaired	Impaired	Unimpaired	P
QLQ-C30					
Physical functioning[§]	94.4 (7.8)	89.6 (12.2)	70.0 (16.2)	88.3 (15.3)	0.002
Social functioning[§]	72.2 (25.1)	79.6 (24.4)	58.3 (13.9)	85.7 (20.7)	0.004
Cognitive functioning[§]	66.7 (36.5)	82.7 (24.0)	66.7 (14.9)	78.6 (21.5)	0.466
Global quality of life[¶]	72.2 (16.4)	75.9 (17.2)	62.5 (25.7)	78.7 (18.1)	0.056
Fatigue[#]	48.1 (26.9)	26.5 (24.4)	50.0 (21.9)	22.7 (23.1)	0.062
HSCL-25	16.4 (10.5)	12.2 (13.2)	22.4 (20.1)	9.0 (9.3)	0.008
PSS	26.8 (9.1)	21.9 (7.4)	27.7 (5.2)	20.0 (6.2)	0.019
POMS					
Total score	17.7 (9.8)	16.5 (15.2)	19.8 (9.4)	11.1 (7.8)	0.012
Fatigue subscale	2.8 (3.1)	2.9 (4.8)	4.3 (3.3)	1.8 (2.5)	0.020
MOS-cog	73.6 (17.9)	78.1 (17.5)	66.7 (17.7)	77.3 (16.3)	0.177
IES			33.0 (17.3)	23.6 (8.1)	0.291

NART = Dutch version of the National Adult Reading Test; AC = doxorubicin (Adriamycin), cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; QLQ-C30 = European Organization for Research and Treatment of Cancer Health-Related Quality-of-Life Questionnaire: scores range from 0 to 100, higher score indicates [§]better functioning, [¶]better quality of life, or [#]more symptoms; HSCL-25 = Hopkins Symptom Checklist–25: scores range from 0 to 100, higher score indicates higher levels of anxiety and depression; PSS = Perceived Stress Scale: scores range from 10 to 50, higher scores indicate higher levels of perceived stress; POMS = Profile of Mood States, higher scores indicate more problems; MOS-cog = Cognitive Functioning Scale of the Medical Outcomes Study, lower scores indicate more problems; IES = Impact of Event Scale, higher scores indicate more distress.
Impairment of BC patients as classified using multivariate normative comparison. Values indicate mean ± SD unless indicated otherwise. P-values indicate overall group differences at T2 adjusted for scores at T1. Differences are considered statistically significant at a critical alpha value of 0.01.
[a]Four or six cycles.
[b]Three or six cycles.
[c]Four cycles AC followed by four or 12 cycles of paclitaxel.
[d]Three or six cycles.

comparable to other studies.[5] Because all women in the BC + SYST group were postmenopausal at follow-up, we could not study the effects of post-treatment menopausal status on cognitive function.

Another limitation is the number of comparisons performed relative to the sample size. We have applied corrections for multiple comparisons by lowering the critical alpha and by using MNC. However, the secondary analyses in the impaired patients should be considered exploratory. Further studies should include larger samples to allow for further investigation of factors that identify patients at risk of developing CRCI.

Future analyses of the MRI data collected in this sample should show whether a neurobiological substrate underlies the finding of cognitive impairment in BC patients.

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Appendix

Supplementary Table 1
Description of Patient-Reported Outcomes and Neuropsychological Tests

Questionnaire	Domain
European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–C30 (QLQ-C30) (Aaronson et al., 1993)	Health-related quality of life
Hopkins Symptom Checklist–25 (Hesbacher, Rickels, Morris, Newman, and Rosenfeld, 1980)	Anxiety and depression
Profile of Mood States (Wald and Mellenbergh, 1990)	Mood state
Perceived Stress Scale (Cohen, Kamarck, and Mermelstein, 1983)	Perceived stress
Trauma Screening Questionnaire (Dekkers, Olff, and Näring, 2010)	Previous traumatic experiences/post-traumatic stress disorder
Cognitive Functioning Scale–Revised of the Medical Outcomes Study (Stewart, Ware, Sherbourne, and Wells, 1992)	Cognitive complaints
Ten-Item Personality Inventory (Gosling, Rentfrow, and Swann, 2003)	Personality dimensions
Neuropsychological Test	**Outcome Measure**
Controlled Oral Word Association test (Benton and Hamsher, 1989) (COWAT)	Number of words beginning with specified letter mentioned within one minute
Behavioral Assessment of the Dysexecutive Syndrome–Zoo Map Test (Wilson, Alderman, Burgess, Emslie, and Evans, 1996) (BADS)	Profile score
Trail Making Test part B (Reitan, 1958) (TMT-B)	Completion time for the task
Eriksen Flanker Task (Eriksen and Eriksen, 1974)	Reaction time congruent trials
	Reaction time perceptually incongruent trials
	Reaction time response incongruent trials
Visual Reaction Time Test (Alpherts and Aldenkamp, 1994) (VRT)	Reaction time dominant hand
	Reaction time nondominant hand
Digit Span of the Wechsler Adult Intelligence Scale (WAIS)-III (Wechsler, 2000)	Number of correct responses
Visual Reproduction Test of the Wechsler Memory Scale–Revised (Wechsler, 1987)	Total score immediate recall
	Total score delayed recall
Hopkins Verbal Learning Test–Revised (Benedict, Schretlen, Groninger, and Brandt, 1998) (HVLT)	Number correct responses immediate recall
	Number correct responses delayed recall
	Number correct responses delayed recognition
Digit Symbol-Coding Test of the WAIS-III (Wechsler, 2000)	Number of correctly substituted digits
Trail Making Test part A (Reitan, 1958) (TMT-A)	Completion time for the task
Finger tapping (Alpherts and Aldenkamp, 1994)	Number of taps dominant hand
	Number of taps nondominant hand