Chemotherapy and Post-traumatic Stress in the Causation of Cognitive Dysfunction in Breast Cancer Patients

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Abstract

Background: Cancer-related cognitive dysfunction has mostly been attributed to chemotherapy; this explanation, however, fails to account for cognitive dysfunction observed in chemotherapy-naïve patients. In a controlled, longitudinal, multisite study, we tested the hypothesis that cognitive function in breast cancer patients is affected by cancer-related post-traumatic stress.

Methods: Newly diagnosed breast cancer patients and healthy control subjects, age 65 or younger, underwent three assessments within one year, including paper-and-pencil and computerized neuropsychological tests, clinical diagnostics of post-traumatic stress disorder (PTSD), and self-reported cognitive function. Analysis of variance was used to compare three groups of participants—patients who did or did not receive chemotherapy and healthy control subjects—on age- and education-corrected cognitive performance and cognitive change. Differences that were statistically significant after correction for false discovery rate were investigated with linear mixed-effects models and mediation models. All statistical tests were two-sided.

Results: Of 226 participants (166 patients and 60 control subjects), 206 completed all assessment sessions (attrition: 8.8%). Patients demonstrated overall cognitive decline (group*time effect on composite z-score: –0.13, $P = .04$) and scored consistently worse on Go/Nogo errors. The latter effect was mediated by PTSD symptoms (mediation effect: $B = 0.15$, 95% confidence interval = 0.02 to 0.38). Only chemotherapy patients showed declined reaction time on a computerized alertness test. Overall cognitive performance correlated with self-reported cognitive problems at one year ($_T = –0.11$, $P = .02$).

Conclusions: Largely irrespective of chemotherapy, breast cancer patients may encounter very subtle cognitive dysfunction, part of which is mediated by cancer-related post-traumatic stress. Further factors other than treatment side effects remain to be investigated.

Many patients with breast or other non–nervous system cancers report cognitive dysfunction (1,2), and some are considerably burdened by it (3–5). Based on evidence of impaired performance on neuropsychological tests after chemotherapy (6), which was bolstered by reports of structural and functional brain anomalies after cytostatic treatment (7), neurotoxicity of chemotherapy has been the prime suspect to cause the condition colloquially termed chemobrain (8–14). The singular role of chemotherapy neurotoxicity for cognitive dysfunction in cancer patients, however, has been questioned by findings of cognitive dysfunction in patients whose systemic treatment had not yet begun (15–24) or who were managed without chemotherapy (25–27). Recent investigations have linked pretreatment cognitive impairment to inflammatory processes caused by the tumor, with as yet equivocal results (15,28,29).

Effects of having cancer on cognitive function are to be expected even if no adverse effects of medications were to occur. It seems very unlikely that distress, sleep problems, and prolonged sick leave, among other factors associated with having cancer, do not impact the brain, which, as a highly dynamic and plastic organ, is susceptible to all experience and subtly changes in interaction with it. In research on cancer-related cognitive dysfunction, however, other factors than medication side effects have comparatively rarely been investigated (30–35). Particularly, although memory and attention impairments are symptoms of many mental diseases (36), which are highly prevalent in cancer patients (37), psychological morbidity has merely been assessed with self-report screening instruments and regarded as a confounder in most studies.

The Cognition in Breast Cancer Patients: The Impact of Cancer-Related Stress (Cognicares) study was designed to test the hypothesis that cognitive dysfunction in breast cancer patients is mediated by post-traumatic stress. Many breast cancer patients experience symptoms of post-traumatic stress disorder (PTSD) (38–41), and there is abundant evidence that PTSD and PTSD symptoms impact the brain (42–48) and cognitive functioning (49–51). Two previous articles on the Cognicares study focused on PTSD symptoms (39) and pretreatment cognitive function (13). Here, we report on cognitive performance and its change in dependence of chemotherapy and PTSD symptoms throughout the first year after diagnosis of breast cancer.

Methods

Participants and Enrollment

Women diagnosed with yet untreated stage 0 to IIIc breast cancer were eligible for participation if they were between age 18 and 65 years, proficient in German, free of substance abuse, without history of neurological or psychotic disorder or systemic treatment for any cancer. Women who had undergone breast imaging with negative result at one of the study centers, had never had cancer, and otherwise met the above-mentioned criteria were eligible for the control group. Participants were enrolled as previously described (13). Written informed consent was obtained from all participants. The study was approved by the ethics committee of the Ludwig Maximilian University of Munich and is registered at ClinicalTrials.gov, registration number NCT01264562 (52).

Assessment Proceedings

Three 120- to 150-minute assessment sessions were scheduled; the first (T1) prior to primary surgery or neoadjuvant chemotherapy for breast cancer patients and a minimum of one week after negative breast imaging for control subjects; the second (T2) a minimum of one week after completion of chemotherapy or at matched intervals after T1, and the third (T3) one year after T1. Assessments were conducted between January 2011 and

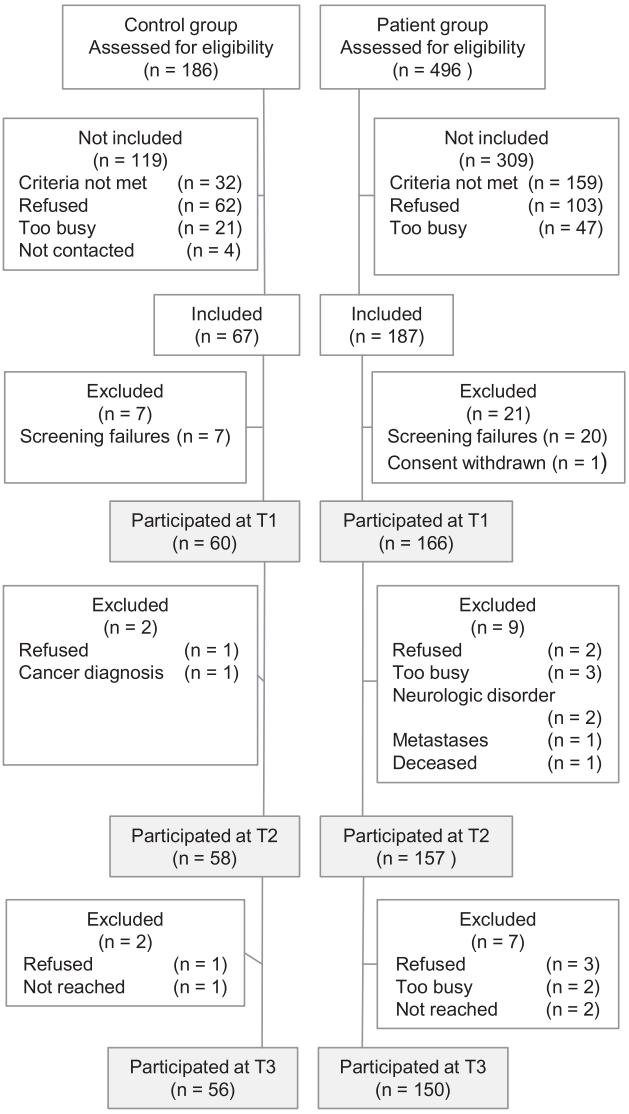

Figure 1. Flow diagram of participant enrollment and attrition. T1 = baseline assessment, before the start of therapy for patients; T2 = assessment after completion of chemotherapy or at matched intervals; T3 = assessment approximately one year after baseline.

Table 1. Demographic and clinical characteristics*

Characteristic	No. of control subjects (%) (T1, T2: n = 58; T3: n = 56)	No. of nonchemotherapy patients (%) (T1, T2: n = 66; T3: n = 62)	No. of chemotherapy patients (%) (T1, T2: n = 91; T3: n = 88)	*P*
Age at T1, y				
Mean (SD)	52.3 (1.7)	53.4 (7.7)	47.7 (9.3)	<.001†
Range	27.3–64.9	34.1–65.6	21.8–65.7	
Educational level‡				.70§
Low	7 (12.1)	11 (16.7)	14 (15.4)	
Medium	29 (50.0)	26 (39.4)	32 (35.2)	
High	8 (13.8)	9 (13.6)	13 (14.3)	
University degree	14 (24.1)	20 (30.3)	32 (35.2)	
Estimated premorbid IQ at T1, mean (SD)	115.5 (13.6)	115.1 (13.7)	110.7 (13.5)	.04†
Living without a partner (T1)	9 (15.5)	20 (30.3)	34 (37.4)	.02§
Non-native speakers of German	2 (3.4)	4 (6.1)	12 (13.2)	.10‖
Hormone replacement therapy ever	13 (22.4)	12 (18.2)	13 (14.3)	.44§
AJCC tumor stage (74)				<.001‖
0	n/a	11 (16.7)	0	
I	n/a	41 (62.1)	25 (27.5)	
II	n/a	14 (21.2)	51 (56.0)	
III	n/a	0	15 (16.5)	
Current antiestrogen therapy				
T2	n/a	55 (83.3)	34 (37.6)	<.001¶
T3	n/a	50 (80.7)	65 (73.9)	.33¶
Occupational status: Gainfully employed or self-employed				
T1	43 (74.1)	52 (78.8)	74 (81.3)	.58§
T2	43 (74.1)	50 (75.8)	73 (80.2)	.32§
T3	39 (69.6)	42 (67.7)	72 (81.8)	.04§
On sick leave (% of gainfully employed or self-employed subjects)				
T2	4 (9.3)	13 (26.0)	54 (74.0)	<.001¶
T3	2 (5.1)	3 (7.1)	21 (29.2)	.008¶
Menopausal status				
T1				.03§
Premenopausal	23 (39.7)	28 (42.4)	53 (58.2)	
Peri- or postmenopausal	29 (50.0)	37 (56.1)	32 (35.2)	
Undetermined	6 (10.3)	1 (1.5)	6 (6.6)	
T2				<.001§
Premenopausal	22 (37.9)	14 (21.2)	3 (3.3)	
Peri- or postmenopausal	31 (53.4)	51 (77.3)	87 (95.6)	
Undetermined	5 (8.6)	1 (1.5)	1 (1.1)	
T3				<.001§
Premenopausal	20 (35.7)	9 (14.5)	5 (5.7)	
Peri- or postmenopausal	31 (55.4)	53 (85.5)	82 (93.2)	
Undetermined	5 (8.9)	0	1 (1.1)	
Current medication potentially affecting brain function#				
T1	17 (29.3)	19 (28.8)	20 (22.0)	.51§
T2	15 (25.9)	18 (27.3)	27 (29.7)	.87§
T3	16 (28.6)	22 (33.8) missing: n = 1	22 (25.0)	.34§
No. of current PTSD symptoms, mean (SD)				
T1	0.4 (1.1)	3.7 (3.0)	3.6 (3.1)	<.001†
T2	0.4 (1.1)	2.6 (2.7)	2.8 (3.0)	<.001†
T3	0.4 (0.9)	2.3 (3.6)	2.5 (3.0)	<.001†
Depression score, mean (SD)**				
T1	2.9 (2.6)	5.8 (3.7)	6.2 (3.7)	<.001†
T2	3.7 (3.5)	4.6 (3.8) missing: n = 1	5.6 (4.2)	.01†
T3	2.7 (3.0)	4.2 (4.5)	4.7 (4.5) missing: n = 2	.03†
EORTC-QLQ-CF, mean (SD)††				
T1	87.4 (20.3)	65.2 (29.5)	68.7 (27.1)	<.001†
T2	86.2 (22.3)	71.2 (26.2)	70.5 (28.2)	<.001†
T3	87.5 (19.9)	78.8 (21.6)	75.2 (25.6)	.003†

(continued)

Table 1. (continued)

Characteristic	No. of control subjects (%) (T1, T2: n = 58; T3: n = 56)	No. of nonchemotherapy patients (%) (T1, T2: n = 66; T3: n = 62)	No. of chemotherapy patients (%) (T1, T2: n = 91; T3: n = 88)	*P*
FEDA, mean (SD)‡‡				
T1	45.5 (12.4)	50.6 (16.3) missing: n = 2	52.2 (18.0) missing: n = 2	.12†
T2	46.8 (13.2) missing: n = 1	52.9 (18.3)	60.0 (19.0)missing: n = 1	<.001†
T3	47.2 (13.2)	48.5 (16.1)	53.0 (19.0)	.19†

*Participants with data beyond baseline are included (n = 215). Data of all 226 participants (including 11 patients who discontinued participation after T1) have previously been published (13). AJCC = American Joint Committee on Cancer; EORTC-QLQ-CF = Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life-Questionnaire C30; FEDA = Questionnaire of Experienced Deficits of Attention; IQ = intelligence quotient; PTSD = post-traumatic stress disorder; T1 = baseline assessment, before the start of therapy for patients; T2 = assessment after completion of chemotherapy or at matched intervals; T3 = assessment approximately one year after baseline.

†Kruskal-Wallis analysis of variance was used to test the differences between the three groups.

‡Low, Hauptschulabschluss; medium, Realschulabschluss; high, Fachhochschulreife or Abitur.

§Pearson's chi-square test was used for comparisons of the three groups.

||Fisher-Freeman-Halton Exact Test was used for comparisons.

¶Pearson's chi-square test was used for comparisons of two patient groups.

#Medications considered to potentially affect brain function: antidepressants, sedatives, benzodiazepines, neuroleptics, antihypertensives, antiphlogistics, antirheumatics, uricostatics, and glucocorticoids.

**Based on PHQ-D depression scale; scores range from 0 to 27, with higher scores reflecting more depression.

††Scores range from 0 to 100, with higher scores reflecting better cognitive functioning.

‡‡Scores range from 27 to 135, with higher scores reflecting more attentional problems.

October 2014 by Master's-level psychologists. Participants were compensated with 15 Euros for each assessment session.

Measures

Demographic and clinical data were collected from the participants and from medical records. Cognitive function was assessed with paper-and-pencil (53–56) and computerized tests (57). Alternate forms of the Verbal Learning and Memory Test (VLMT) (55) were used. Premorbid intelligence was estimated with a language-based test (58). Subjective cognitive functioning was measured with the Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire C30, version 3.0 (EORTC-QLQ-CF) (59,60) and the Questionnaire of Experienced Deficits of Attention (FEDA) (61). PTSD symptoms were diagnosed with the Structured Clinical Interview for DSM-IV (SCID) (62). Diagnostic procedures for PTSD have already been described (13,39). Briefly, in addition to cancer-related PTSD symptoms, which were fully assessed at all three time points, the worst non-breast cancer-related traumatic event was assessed at T1. At T2 and T3, non-breast cancer-related traumatic events were assessed if they had newly happened, and non-breast cancer-related, mostly long-standing PTSD symptoms diagnosed at previous assessments were treated as persistent. The German version of the Patient Health Questionnaire (PHQ-D) (63–64) was used to measure depression and to screen for mental disorders. All instruments were validated.

Statistical Analyses

Indices of cognitive function derived from the neuropsychological tests have earlier been described in detail (13). As in the key analyses of the previous report, commission errors and omission errors were aggregated in an error score for the Divided Attention Test and the Go/Nogo Test, resulting in 18 indices of specific cognitive abilities.

Outliers, even if they are legitimate data points, distort descriptive statistics and reduce the power of statistical tests. Therefore, in the raw cognitive scores, extreme outliers (data points more than 3*interquartile range below the first quartile or above the third quartile) were winsorized; that is, they were replaced with the lowest or highest value not considered an extreme outlier (65–67).

Winsorized cognitive raw scores were adjusted for age and dummy-coded education, and z-standardized. Whenever quadratic relations of cognitive scores and age were found, a quadratic term for age was added in the regression. For each of the time points, the mean across all age- and education-adjusted cognitive indices was calculated as a composite score of overall cognitive performance.

To determine cognitive change, T2 and T3 cognitive scores were adjusted for T1 (68) and additionally for age and education. Again, if appropriate, quadratic terms of T1 cognitive scores and age were included. The mean of the resulting z-standardized residuals across all cognitive indices served as a composite score of cognitive change in relation to baseline at the respective time point.

Analysis of variance (ANOVA) was used to compare three participant groups—control subjects, nonchemotherapy patients, and chemotherapy patients—on age- and education-adjusted scores of cognitive performance and cognitive change at T2 and T3. Multiple testing was addressed with a false discovery rate (FDR) correction optimized for grouped hypotheses (69), which was performed for four groups of 19 hypotheses each: differences between the participant groups on cognitive performance at T2, cognitive performance at T3, cognitive change at T2, and cognitive change at T3; each group with 19 indices, including a composite score. An FDR of 20% was accepted. Cognitive indices that showed statistically significant differences of either performance or change after FDR correction were investigated with linear mixed-effects models. Winsorized cognitive raw scores of the respective index, or, for the composite score, the mean across all winsorized cognitive raw scores standardized by the control subjects' scores at T1, were entered as dependent variables. Predictors were preselected based on

Table 2. Neuropsychological test results, raw scores*

Cognitive indices	Control subjects			Nonchemo patients			Chemotherapy patients		
	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)
Attention									
TAP Alertness: RT condition 1 (57)	286	295	291	276	286	289	280	294	299
Median, ms	(60)	(60)	(49)	(46)	(57)	(55)	(55)	(67)	(70)
(intrinsic alertness)	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 91	n = 86	n = 87
TAP Alertness: RT condition 2 (57)	295	296	288	272	279	285	279	291	293
Median, ms	(62)	(67)	(55)	(49)	(52)	(62)	(55)	(67)	(70)
(phasic arousal)	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 91	n = 86	n = 87
TAP Alertness: SD of RT, condition 1 (57)	45	47	40	43	46	47	47	47	48
Median, ms	(22)	(24)	(16)	(22)	(22)	(20)	(25)	(23)	(26)
(stability of intrinsic alertness)	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 91	n = 86	n = 87
TAP Alertness: SD of RT, condition 2 (57)	46	45	42	42	44	43	41	45	44
Median, ms	(20)	(18)	(18)	(20)	(19)	(20)	(18)	(22)	(23)
(stability of phasic arousal)	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 91	n = 86	n = 87
TAP Alertness: Index phasic alertness (57)	−0.03	0.00	0.02	0.01	0.02	0.02	0.00	0.01	0.02
Higher values indicate better function	(0.11)	(0.10)	(0.09)	(0.08)	(0.08)	(0.10)	(0.09)	(0.09)	(0.10)
(phasic alertness)	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 91	n = 86	n = 87
TAP Divided attention: No. of errors (57)	3.55	3.21	2.82	3.48	3.32	3.40	3.54	2.51	2.73
(divided attention: accuracy)	(3.23)	(3.30)	(3.26)	(3.27)	(3.19)	(3.50)	(3.75)	(2.26)	(2.46)
	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 90	n = 86	n = 86
TAP Go/Nogo: RT (57)	432	431	441	431	444	437	431	442	458
Median, ms	(70)	(65)	(70)	(72)	(61)	(68)	(75)	(69)	(77)
(behavioral control: processing speed)	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 90	n = 86	n = 85
TAP Go/Nogo: SD of RT (57)	73	73	71	74	77	76	81	82	79
Median, ms	(21)	(26)	(23)	(22)	(20)	(20)	(22)	(27)	(23)
(behavioral control: stability of performance)	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 90	n = 86	n = 85
TAP Go/Nogo: No. of errors (57)	0.45	0.62	0.38	0.89	0.80	0.65	1.04	0.74	0.87
(behavioral control: accuracy)	(0.84)	(0.99)	(0.71)	(1.06)	(0.95)	(1.09)	(1.27)	(1.05)	(1.18)
	n = 58	n = 58	n = 55	n = 65	n = 66	n = 62	n = 90	n = 86	n = 85
Trail making test A (TMT-A) (53)	29.66	28.03	26.80	29.15	29.23	27.69	29.97	29.83	27.55
Completion time in seconds	(8.68)	(8.22)	(6.66)	(9.59)	(10.18)	(9.53)	(9.59)	(10.68)	(9.66)
(visual search, psychomotor speed)	n = 58	n = 58	n = 56	n = 66	n = 66	n = 62	n = 90	n = 90	n = 88
Memory									
Digit span forward (56)	7.91	8.07	8.36	7.83	8.15	8.21	7.58	7.90	8.02
No. of correctly repeated digit strings	(1.72)	(1.79)	(1.61)	(1.85)	(1.92)	(1.91)	(1.97)	(1.96)	(1.83)
(short term memory)	n = 58	n = 58	n = 56	n = 66	n = 66	n = 62	n = 91	n = 90	n = 88
Digit span backward (56)	6.93	7.31	7.25	6.72	6.82	7.05	6.80	7.32	7.51
No. of correct inversely repeated digit strings	(1.92)	(2.03)	(2.24)	(2.10)	(2.03)	(2.05)	(1.96)	(2.17)	(2.02)
(working memory)	n = 58	n = 58	n = 56	n = 65	n = 66	n = 62	n = 91	n = 90	n = 88
Verbal learning and memory test (VLMT)	56.72	61.10	59.75	55.88	60.36	57.34	56.96	61.56	59.84
Learning efficiency (55)	(6.90)	(8.33)	(8.49)	(8.55)	(8.46)	(9.06)	(8.94)	(7.31)	(8.48)
No. of correctly reported words, sum of trails 1–5	n = 58	n = 58	n = 56	n = 65	n = 66	n = 62	n = 90	n = 90	n = 88
(verbal memory)									
Verbal learning and memory test (VLMT) free	12.36	13.11	12.64	11.83	12.74	12.08	12.54	13.26	12.69
recall (55)	(2.97)	(2.62)	(3.26)	(2.70)	(2.28)	(2.89)	(2.57)	(2.13)	(2.53)
No. of correctly reported words after delay	n = 58	n = 57	n = 56	n = 65	n = 66	n = 62	n = 91	n = 90	n = 88)
(verbal memory)									
Verbal learning and memory test (VLMT)	1.40	0.98	1.38	1.43	1.21	1.53	1.10	0.82	1.32
consolidation (55)	(2.25)	(1.74)	(2.14)	(1.88)	(1.68)	(1.89)	(1.70)	(1.50)	(1.99)
Difference of the last trial prior to the delay and the delayed trial, ie, No. of words lost after the delay	n = 58	n = 57	n = 56	n = 65	n = 66	n = 62	n = 90	n = 90	n = 88
(verbal memory)									
Executive function									
Trail making test B (TMT-B) (53)	65.91	63.02	62.52	68.50	65.74	60.37	68.33	65.44	61.58
Completion time in seconds	(20.76)	(19.94)	(20.24)	(22.94)	(24.14)	(17.66)	(25.56)	(26.32)	(19.68)
(visual search, executive processing speed)	n = 58	n = 58	n = 56	n = 66	n = 66	n = 62	n = 89	n = 90	n = 88

(continued)

Table 2. (continued)

Cognitive indices	Control subjects			Nonchemo patients			Chemotherapy patients		
	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)
Regensburg word fluency test (RWT), lexical search (54)	19.16 (4.91)	20.52 (6.08)	21.80 (6.45)	19.82 (6.38)	21.70 (7.14)	22.06 (6.75)	19.09 (5.74)	20.50 (6.43)	21.55 (7.02)
No. of correctly produced words (lexical verbal fluency)	n = 58	n = 58	n = 56	n = 65	n = 66	n = 62	n = 91	n = 90	n = 88
Regensburg word fluency test (RWT), semantic search (54)	23.60 (5.37)	24.36 (5.33)	24.95 (4.95)	23.51 (6.99)	25.14 (6.92)	25.13 (7.68)	25.40 (8.00)	25.00 (7.54)	25.74 (7.90)
No. of correctly produced words (semantic verbal fluency)	n = 58	n = 58	n = 56	n = 65	n = 66	n = 62	n = 90	n = 90	n = 88

*Please note that the data have been winsorized. Participants with data beyond baseline are included (n = 215). Data of all 226 participants (including 11 patients who discontinued participation after T1) have previously been published (13). RT = reaction time; T1 = baseline assessment, before the start of therapy for patients; T2 = assessment after completion of chemotherapy or at matched intervals; T3 = assessment approximately one year after baseline; TAP = Tests of Attentional Performance.

theoretical considerations and forced into the models. Mediation models were used to investigate whether group effects were mediated by PTSD symptoms. The following variables were included: participant group (independent variable); number of PTSD symptoms (mediator); winsorized cognitive raw scores of the respective index or, for the composite score, the mean across all winsorized cognitive raw scores standardized by the control subjects' scores at T1 (dependent variable), and all other variables used in the linear mixed-effects models except time and its interactions (covariates). Statistical significance of the regression coefficients and the mediation effect was tested with a *t*-statistic and a nonparametric bootstrapping procedure (10 000 repetitions), respectively, which are included in the INDIRECT macro for SPSS by Preacher and Hayes (70). Kendall tau ($_T$) rank correlation was used to test bivariate associations of cognitive indices that showed effects of participant group with PTSD symptoms and self-reported cognitive function.

We followed International Cognition and Cancer Task Force (ICCTF) recommendations (12) and defined individual cognitive impairment by the number of age- and education-adjusted cognitive test scores 1.5 and 2 standard deviations below the mean of the control group, applying a definition that rendered an impairment rate of 5% in control subjects at T1 (13); namely, five or more scores below 1.5 standard deviations and/or four or more scores below 2 standard deviations. The relative risk of cognitive impairment for patients was calculated.

The study was powered to detect 5% of explained variance with 80% power at a statistical significance level of 5%. IBM SPSS Statistics 22 and 23 (Armonk, NY: IBM Corp.); the software R (71), packages lme4 (72), and lmerTest (73); and the mediation procedure macro INDIRECT for SPSS (70) were utilized. All statistical tests were two-sided with a 5% statistical significance level.

Results

Participants, Timing of Assessments, and Outlying Data

Participant enrollment has previously been described (13). Of 226 participants (166 patients and 60 control subjects) who participated at T1, 215 and 206 also completed T2 and T3 assessments, respectively (attrition: n = 20, 8.8%) (Figure 1). Excluded participants did not statistically significantly differ from continuers on age, education, AJCC tumor stage (74), number of PTSD symptoms (data not shown), and the age- and education-corrected composite cognitive z-score at T1 (mean difference = 0.0003, 95% CI = –0.20 to 0.20, *P* = .82, n = 226). Demographic and clinical characteristics of three participant groups that emerged at T2—control subjects, nonchemotherapy patients, and chemotherapy patients—are given in Table 1 and Supplementary Table 1 (available online). T2 and T3 assessments took place approximately 7.5 months (control subjects: mean/SD = 32.6/2.9 weeks, n = 58; nonchemotherapy patients: mean/SD = 32.2/3.3 weeks, n = 66; chemotherapy patients: mean/SD = 33.9/4.5 weeks, n = 91) and one year (control subjects: mean/SD = 55.1/2.6 weeks, n = 56; nonchemotherapy patients: mean/SD = 54.5/3.3 weeks, n = 62; chemotherapy patients: mean/SD = 55.6/4.0 weeks, n = 88) after T1, and approximately two months (mean/SD = 9.1/5.3 weeks, n = 91) and seven months (mean/SD = 31.0/5.5 weeks, n = 88) after completion of chemotherapy, respectively.

Sixty extreme outliers (0.5 % of all data points) were identified (24, 18, and 18 extreme outliers at T1, T2, and T3, respectively) among the raw scores of the Trail-Making Tests A and B, Verbal Learning and Memory Test consolidation, and all computerized measures except Index phasic alertness and Go/Nogo reaction time. The rate of participants with extreme outliers did not statistically significantly differ between the groups at any time point (Fisher-Freeman-Halton Exact Test, data not shown). All extreme outliers were winsorized.

Comparisons of Participant Groups on Cognitive Function

Winsorized cognitive raw data, age- and education-adjusted performance scores, and age- and education-adjusted cognitive change scores are shown in Tables 2 through 4, respectively. Cognitive change at T3 is also displayed in Figure 2.

No differences of age- and education-corrected cognitive performance or cognitive change between the participant groups were detected at T2 (Tables 3 and 4). At T3, however, statistically significant differences of cognitive performance were found on four indices (composite score, Alertness RT condition 1, Alertness SD of RT condition 1, Go/Nogo errors) (Table 3), and these indices were further investigated. Linear mixed-effects model analyses demonstrated effects of participant group on three of these indices (Table 5):

On the composite score, an interaction effect of time with both patient groups (estimate, –0.13 z-values, *P* = .04) indicated

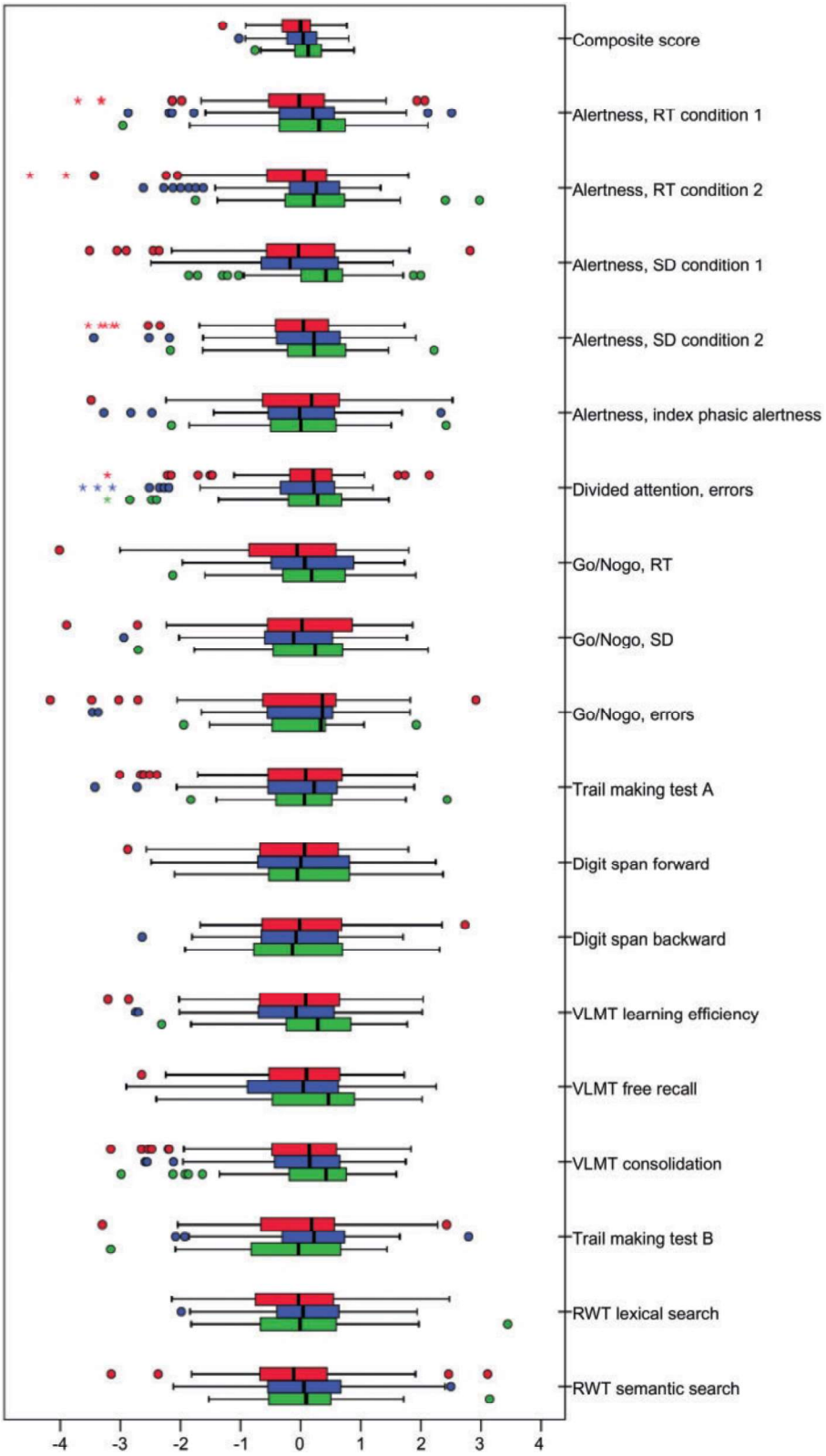

Figure 2. Cognitive change one year after diagnosis relative to baseline. **Red**: chemotherapy patients (n = 88). **Blue**: nonchemotherapy patients (n = 62). **Green**: control subjects (n = 56). Units are z-scores adjusted for baseline scores, age, and education. High scores indicate improvement; low scores indicate decline relative to baseline. **Boxes** represent the first and the third quartile, the **line across the box** represents the median, **whiskers** indicate the farthest data points within 1.5*interquartile range (IQR) from the box, **dots** represent data points between 1.5*IQR and 3*IQR from the box, and **asterisks** represent data points farther than 3*IQR from the box. RT = reaction time; RWT = Regensburg Word Fluency Test; VLMT = Verbal Learning and Memory Test.

Table 3. Cognitive performance in the first year after diagnosis*

	T1†			T2				T3			
Cognitive indices	Control subjects Mean (SD)	Nonchemo patients Mean (SD)	Chemo patients Mean (SD)	Control subjects Mean (SD)	Nonchemo patients Mean (SD)	Chemo patients Mean (SD)	*P*‡	Control subjects Mean (SD)	Nonchemo patients Mean (SD)	Chemo patients Mean (SD)	*P*‡
Composite score	0.02	0.08	–0.07	0.06	0.05	–0.08	.06	0.10	0.04	–0.10	.01§
	(0.37)	(0.44)	(0.48)	(0.38)	(0.39)	(0.40)		(0.38)	(0.45)	(0.42)	
	n = 58	n = 66	n = 91	n = 58	n = 66	n = 90		n = 56	n = 62	n = 88	
Attention											
Alertness: RT condition 1	–0.07	0.19	–0.11	0.00	0.18	–0.14	.13	0.10	0.19	–0.20	.04§
	(1.11)	(0.90)	(0.98)	(0.95)	(0.96)	(1.02)		(0.79)	(0.98)	(1.08)	
	n = 58	n = 65	n = 91	n = 58	n = 66	n = 86		n = 55	n = 62	n = 87	
Alertness: RT condition 2	–0.22	0.25	–0.06	–0.07	0.23	–0.13	.06	0.08	0.17	–0.17	.10
	(1.06)	(0.91)	(0.98)	(1.03)	(0.86)	(1.03)		(0.83)	(1.03)	(1.03)	
	n = 58	n = 65	n = 91	n = 58	n = 66	n = 86		n = 55	n = 62	n = 87	
Alertness: SD of RT, condition 1	0.05	0.16	–0.19	0.05	0.08	–0.09	.51	0.32	0.02	–0.21	.007§
	(0.94)	(0.92)	(1.08)	(1.04)	(0.95)	(0.98)		(0.70)	(0.94)	(1.12)	
	n = 58	n = 65	n = 91	n = 58	n = 66	n = 86		n = 55	n = 62	n = 87	
Alertness: SD of RT, condition 2	–0.13	0.14	0.00	0.04	0.10	–0.10	.45	0.11	0.12	–0.16	.14
	(0.99)	(1.06)	(0.91)	(0.88)	(0.95)	(1.08)		(0.85)	(0.97)	(1.06)	
	n = 58	n = 65	n = 91	n = 58	n = 66	n = 86		n = 55	n = 62	n = 87	
Alertness: Index phasic alertness	–0.28	0.15	0.07	–0.13	0.12	0.00	.39	–0.02	–0.03	0.04	.91
	(1.12)	(0.85)	(0.99)	(1.06)	(0.91)	(1.00)		(0.91)	(1.03)	(1.02)	
	n = 58	n = 65	n = 91	n = 58	n = 66	n = 86		n = 55	n = 62	n = 87	
Divided attention: errors	0.04	0.07	–0.07	–0.06	–0.05	0.07	.68	0.06	–0.11	0.04	.57
	(0.85)	(0.93)	(1.08)	(1.15)	(1.08)	(0.79)		(1.06)	(1.15)	(0.80)	
	n = 58	n = 65	n = 90	n = 58	n = 66	n = 86		n = 55	n = 62	n = 86	
Go/Nogo: RT	0.01	0.01	–0.02	0.15	–0.07	–0.05	.40	0.09	0.14	–0.16	.13
	(0.98)	(0.98)	(1.04)	(0.97)	(0.91)	(1.06)		(0.94)	(0.91)	(1.05)	
	n = 58	n = 65	n = 90	n = 58	n = 66	n = 86		n = 55	n = 62	n = 85	
Go/Nogo: SD of RT	0.21	0.12	–0.22	0.18	0.03	–0.15	.13	0.19	–0.01	–0.12	.19
	(0.93)	(0.98)	(0.99)	(1.06)	(0.81)	(1.05)		(1.04)	(0.90)	(1.01)	
	n = 58	n = 65	n = 90	n = 58	n = 66	n = 86		n = 55	n = 62	n = 85	
Go/Nogo: errors	0.38	0.01	–0.22	0.10	–0.06	–0.02	.64	0.26	0.04	–0.20	.02§
	(0.73)	(0.89)	(1.10)	(0.98)	(0.92)	(1.04)		(0.65)	(1.00)	(1.12)	
	n = 58	n = 65	n = 90	n = 58	n = 66	n = 86		n = 55	n = 62	n = 85	
Trail making test A (TMT-A)	0.03	0.15	–0.14	0.18	0.11	–0.20	.04‖	0.13	0.08	–0.14	.20
	(0.80)	(1.03)	(1.07)	(0.78)	(1.03)	(1.05)		(0.65)	(1.06)	(1.10)	
	n = 58	n = 66	n = 90	n = 58	n = 66	n = 90		n = 56	n = 62	n = 88	
Memory											
Digit span forward	0.11	0.08	–0.11	0.04	0.09	–0.10	.47	0.11	0.08	–0.13	.25
	(0.90)	(0.99)	(1.06)	(0.95)	(0.98)	(1.02)		(0.86)	(1.07)	(1.00)	
	n = 58	n = 66	n = 91	n = 58	n = 66	n = 90		n = 56	n = 62	n = 88	
Digit span backward	0.13	0.06	–0.05	0.14	–0.10	–0.02	.39	0.01	–0.06	0.04	.83
	(0.96)	(1.04)	(0.97)	(0.93)	(0.94)	(1.06)		(1.07)	(0.98)	(0.95)	
	n = 58	n = 65	n = 91	n = 58	n = 66	n = 90		n = 56	n = 62	n = 88	
VLMT learning efficiency	0.07	0.00	–0.06	0.10	0.03	–0.09	.52	0.20	–0.09	–0.06	.21
	(0.83)	(1.00)	(1.02)	(1.22)	(0.95)	(0.84)		(1.05)	(0.96)	(0.96)	
	n = 58	n = 65	n = 90	n = 58	n = 66	n = 90		n = 56	n = 62	n = 88	
VLMT free recall	0.08	–0.08	–0.01	0.12	–0.04	–0.05	.58	0.16	–0.05	–0.07	.38
	(1.10)	(1.01)	(0.85)	(1.19)	(0.94)	(0.89)		(1.22)	(0.94)	(0.85)	
	n = 58	n = 65	n = 91	n = 57	n = 66	n = 90		n = 56	n = 62	n = 88	
VLMT consolidation	–0.04	–0.02	0.03	0.07	–0.06	0.00	.76	0.08	–0.01	–0.04	.76
	(1.13)	(1.01)	(0.87)	(1.06)	(1.05)	(0.91)		(1.09)	(0.92)	(0.98)	
	n = 58	n = 65	n = 90	n = 57	n = 66	n = 90		n = 56	n = 62	n = 88	
Executive function											
Trail making test B (TMT-B)	0.16	0.08	–0.20	0.18	0.09	–0.19	.06	0.02	0.20	–0.15	.10
	(0.85)	(0.96)	(1.10)	(0.74)	(1.01)	(1.08)		(0.99)	(0.92)	(1.02)	
	n = 58	n = 66	n = 89	n = 58	n = 66	n = 90		n = 56	n = 62	n = 88	
RWT lexical search	–0.02	0.07	–0.06	–0.02	0.15	–0.10	.30	0.03	0.05	–0.05	.79
	(0.89)	(1.08)	(0.97)	(0.95)	(1.07)	(0.95)		(0.98)	(0.97)	(1.01)	
	n = 58	n = 65	n = 91	n = 58	n = 66	n = 90		n = 56	n = 62	n = 88	

(continued)

Table 3. (continued)

Cognitive indices	T1† Control subjects Mean (SD)	T1† Nonchemo patients Mean (SD)	T1† Chemo patients Mean (SD)	T2 Control subjects Mean (SD)	T2 Nonchemo patients Mean (SD)	T2 Chemo patients Mean (SD)	*P*‡	T3 Control subjects Mean (SD)	T3 Nonchemo patients Mean (SD)	T3 Chemo patients Mean (SD)	*P*‡
RWT semantic search	–0.11 (0.80) n = 58	–0.12 (0.98) n = 65	0.11 (1.09) n = 90	–0.04 (0.81) n = 58	0.06 (1.05) n = 66	–0.01 (1.05) n = 90	.85	–0.04 (0.78) n = 56	–0.01 (1.04) n = 62	0.03 (1.08) n = 88	.92

*z-scores adjusted for age and education. Participants with data beyond baseline are included (n = 215). RT = reaction time; RWT = Regensburg Word Fluency Test; T1 = baseline assessment, before the start of therapy for patients; T2 = assessment after completion of chemotherapy or at matched intervals; T3 = assessment approximately one year after baseline; TAP = Tests of Attentional Performance; VLMT = Verbal Learning and Memory Test.
†T1 comparisons of patient and control data have previously been reported (13).
‡One-way analysis of variance was used for comparisons of the three groups of participants.
§Statistically significant after adaptive Benjamini-Hochberg correction with groups (69).
||Not statistically significant after adaptive Benjamini-Hochberg correction with groups (69).

Table 4. Cognitive change in the first year after diagnosis*

Cognitive indices	T2 Control subjects Mean (SD)	T2 Nonchemotherapy patients Mean (SD)	T2 Chemotherapy patients Mean (SD)	*P*†	T3 Control subjects Mean (SD)	T3 Nonchemotherapy patients Mean (SD)	T3 Chemotherapy patients Mean (SD)	*P*†
Composite score	0.06 (0.32) n = 58	0.00 (0.32) n = 66	−0.04 (0.35) n = 90	.27	0.11 (0.35) n = 56	−0.01 (0.38) n = 62	−0.07 (0.37) n = 88	.02‡
Attention								
Alertness: RT condition 1	0.06 (0.90) n = 58	0.06 (0.99) n = 65	−0.08 (1.03) n = 86	.59	0.16 (0.90) n = 55	0.08 (0.95) n = 61	−0.16 (1.04) n = 87	.12
Alertness: RT condition 2	0.11 (1.01) n = 58	0.06 (0.83) n = 65	−0.12 (1.07) n = 86	.34	0.24 (0.83) n = 55	0.00 (0.92) n = 61	−0.16 (1.09) n = 87	.06
Alertness: SD of RT, condition 1	0.04 (1.03) n = 58	−0.02 (0.99) n = 65	−0.01 (0.96) n = 86	.94	0.33 (0.82) n = 55	−0.11 (0.92) n = 61	−0.13 (1.08) n = 87	.01‡
Alertness: SD of RT, condition 2	0.12 (0.89) n = 58	0.01 (1.00) n = 65	−0.09 (1.03) n = 86	.44	0.19 (0.84) n = 55	0.05 (0.97) n = 61	−0.15 (1.06) n = 87	.11
Alertness: Index phasic alertness	−0.05 (1.00) n = 58	0.07 (0.94) n = 65	−0.02 (1.01) n = 86	.76	0.05 (0.83) n = 55	−0.07 (1.02) n = 61	0.02 (1.06) n = 87	.78
Divided attention: errors	−0.07 (1.24) n = 58	−0.08 (1.02) n = 65	0.11 (0.73) n = 86	.43	0.03 (1.05) n = 55	−0.15 (1.13) n = 61	0.09 (0.82) n = 86	.35
Go/Nogo: RT	0.21 (0.95) n = 58	−0.15 (0.98) n = 65	−0.03 (1.00) n = 86	.12	0.16 (0.84) n = 55	0.11 (0.90) n = 61	−0.18 (1.10) n = 85	.07
Go/Nogo:SD of RT	0.09 (0.94) n = 58	−0.02 (0.83) n = 65	−0.04 (1.12) n = 86	.72	0.12 (0.92) n = 55	−0.08 (0.92) n = 61	−0.02 (1.07) n = 85	.51
Go/Nogo: errors	−0.06 (1.06) n = 58	−0.08 (0.93) n = 65	0.10 (0.97) n = 86	.47	0.10 (0.65) n = 55	0.04 (0.95) n = 61	−0.10 (1.17) n = 85	.46
Trail making test A (TMT-A)	0.17 (0.91) n = 58	0.01 (1.03) n = 66	−0.11 (0.98) n = 89	.24	0.10 (0.80) n = 56	−0.03 (1.00) n = 62	−0.04 (1.07) n = 87	.69
Memory								
Digit span forward	−0.04 (1.10) n = 58	0.07 (0.89) n = 66	−0.02 (0.98) n = 90	.80	0.08 (0.96) n = 56	0.04 (0.96) n = 62	−0.08 (1.02) n = 88	.62

(continued)

Table 4. (continued)

Cognitive indices	T2 Control subjects Mean (SD)	T2 Nonchemotherapy patients Mean (SD)	T2 Chemotherapy patients Mean (SD)	T2 P†	T3 Control subjects Mean (SD)	T3 Nonchemotherapy patients Mean (SD)	T3 Chemotherapy patients Mean (SD)	T3 P†
Digit span backward	0.09	−0.12	0.03	.45	−0.05	−0.07	0.08	.60
	(0.95)	(0.82)	(1.11)		(1.07)	(0.95)	(0.95)	
	n = 58	n = 65	n = 90		n = 56	n = 61	n = 88	
VLMT learning efficiency	0.09	0.00	−0.06	.67	0.21	−0.14	−0.04	.14
	(1.15)	(1.03)	(0.83)		(0.93)	(0.99)	(1.00)	
	n = 58	n = 65	n = 89		n = 56	n = 61	n = 87	
VLMT free recall	0.08	−0.02	−0.04	.74	0.17	−0.06	−0.07	.31
	(1.01)	(0.96)	(0.99)		(1.01)	(0.99)	(0.96)	
	n = 57	n = 65	n = 90		n = 56	n = 61	n = 88	
VLMT consolidation	0.10	−0.07	−0.01	.65	0.14	−0.04	−0.06	.45
	(0.99)	(1.04)	(0.94)		(0.98)	(0.97)	(1.00)	
	n = 57	n = 65	n = 89		n = 56	n = 61	n = 87	
Executive function								
Trail making test B (TMT-B)	0.05	0.00	−0.04	.87	−0.17	0.13	0.01	.26
	(0.69)	(1.14)	(1.04)		(1.02)	(0.98)	(0.96)	
	n = 58	n = 66	n = 88		n = 56	n = 62	n = 86	
RWT lexical search	−0.02	0.12	−0.07	.50	0.05	0.01	−0.04	.87
	(0.97)	(1.02)	(0.97)		(1.02)	(0.91)	(1.02)	
	n = 58	n = 65	n = 90		n = 56	n = 61	n = 88	
RWT semantic search	0.02	0.13	−0.11	.32	0.09	0.06	−0.10	.44
	(0.88)	(1.09)	(0.97)		(0.91)	(1.04)	(0.99)	
	n = 58	n = 65	n = 89		n = 56	n = 61	n = 87	

*z-scores adjusted for baseline test results, age, and education. Positive scores indicate improvement and negative scores indicate deterioration relative to the entire sample. RT = reaction time; RWT = Regensburg Word Fluency Test; T2 = assessment after completion of chemotherapy or at matched intervals; T3 = assessment approximately one year after baseline; TAP = Tests of Attentional Performance; VLMT = Verbal Learning and Memory Test.
†One-way analysis of variance was used for comparisons of the three groups of participants.
‡Not statistically significant after adaptive Benjamini-Hochberg correction with groups (69).

decline of overall performance in patients relative to control subjects at T3, which concurred with improvement of the entire sample at T2 and T3, as signified by the effects of time alone (T2: estimate, 0.12 z-values, $P = .004$; T3: estimate, 0.21 z-values, $P < .001$). On Alertness RT condition 1, an interaction effect of time with chemotherapy group ($P = .03$) indicated declined performance of chemotherapy patients relative to nonchemotherapy patients and control subjects at T3. On Go/Nogo errors, effects of both patient groups (nonchemotherapy patients, $P = .01$; chemotherapy patients, $P < .001$) indicated consistently worse performance of patients compared with control subjects, while an interaction effect of time with chemotherapy group signified improvement of chemotherapy patients relative to nonchemotherapy patients and control subjects at T2 ($P = .01$). No effects of antiestrogen therapy were found in any of the linear mixed-effects model analyses (Table 5).

The composite score of cognitive performance correlated statistically significantly with the FEDA ($_T = -0.11$, $P = .02$, n = 206) at T3. No other statistically significant correlations of self-reported cognitive function (Table 1) with any of the measures of cognitive performance that differed between the participant groups at T3 emerged (data not shown).

Individual cognitive impairment was found in three control subjects (5.3%, n = 57), two nonchemotherapy patients (3.0%, n = 66), and five chemotherapy patients (5.8%, n = 86) at T2; and in four control subjects (7.3%, n = 55), 11 nonchemotherapy patients (17.7%, n = 62), and 15 chemotherapy patients (17.6%, n = 85) at T3. The relative risk (RR) of cognitive impairment was not statistically significantly increased for breast cancer patients (RR = 2.43, 95% CI = 0.89 to 6.65, n = 202 at T3).

Effects of PTSD Symptoms on Cognitive Function

In breast cancer patients, the number of PTSD symptoms decreased from T1 to T3 (Table 1). The distribution of PTSD symptoms was extremely skewed, with 70 (31.0%, n = 226), 82 (38.1%, n = 215), and 97 (47.1%, n = 206) participants not experiencing any PTSD symptoms at T1, T2, and T3, respectively. Correlations of PTSD symptoms with FEDA and EORTC-QLQ-CF scores (Table 1) ranged in magnitude from 0.26 to 0.42 (all $P < .001$, data not shown).

In linear mixed-effects models, PTSD symptoms did not statistically significantly predict any of the four cognitive indices that differed between the participant groups (Table 5). In exploratory nonparametric bivariate analyses, all correlations of composite cognitive change and Go/Nogo errors at T3 with PTSD symptoms at T2 as well as T3 were statistically significant. Statistical significance was retained when control subjects were excluded from the analyses (Table 6). A mediation effect of PTSD symptoms was detected on one of the three indices that showed effects of participant group in linear models: The effect of patient vs control group on Go/Nogo errors at T3 (unstandardized regression coefficient B = 0.52, $P = .04$, n = 193) decreased

Table 5. Predictors of cognitive indices in a two-sided linear mixed-effects models (n = 226)

	Composite score		Alertness, RT condition 1		Alertness, SD of RT condition 1		Go/Nogo errors	
Factors	Estimate* (95% CI)	*P*	Estimate† (95% CI)	*P*	Estimate† (95% CI)	*P*	Estimate‡ (95% CI)	*P*
(Intercept)	–0.008 (–0.21 to 0.20)	.93	295.61 (266.25 to 324.22)	<.001	41.39 (29.25 to 53.67)	<.001	0.48 (–0.10 to 1.07)	.11
Age§	–0.03 (–0.04 to –0.03)	<.001	2.98 (1.98 to 3.98)	<.001	0.97 (0.59 to 1.35)	<.001	0.02 (0.0008 to 0.036)	.047
Age squared‖	–0.0009 (–0.001 to –0.0004)	<.001	0.04 (–0.03 to 0.11)	.23	0.02 (–0.008 to 0.04)	.18	0.0009 (–0.0001 to 0.002)	.09
Educational level: medium¶	–0.01 (–0.16 to 0.14)	.86	3.68 (–17.36 to 24.35)	.74	6.40 (–1.56 to 14.34)	.11	–0.12 (–0.48 to 0.23)	.50
Educational level: high¶	–0.01 (–0.20 to 0.17)	.88	14.49 (–11.89 to 40.83)	.28	8.41 (–1.36 to 18.00)	.09	–0.40 (–0.84 to 0.05)	.08
Educational level: university degree¶	0.15 (–0.01 to 0.31)	.07	3.50 (–19.39 to 26.20)	.76	3.46 (–5.04 to 11.73)	.42	–0.31 (–0.69 to 0.07)	.11
Estimated premorbid IQ§	0.01 (0.008 to 0.02)	<.001	–0.28 (–0.83 to 0.27)	.32	–0.10 (–0.30 to 0.10)	.36	–0.002 (–0.01 to 0.007)	.65
Peri- or postmenopausal status#	0.05 (–0.03 to 0.12)	.24	–10.31 (–21.01 to 0.42)	.06	–1.50 (–6.60 to 3.65)	.57	–0.007 (–0.27 to 0.25)	.96
Medication potentially affecting brain function	–0.02 (–0.10 to 0.06)	.61	–2.95 (–14.13 to 8.00)	.60	–2.35 (–7.44 to 2.65)	.35	0.07 (–0.17 to 0.31)	.57
No. of PTSD symptoms**	–0.008 (–0.02 to 0.004)	.19	–0.43 (–2.16 to 1.30)	.62	0.17 (–0.65 to 0.96)	.68	0.01 (–0.03 to 0.05)	.47
Depression score**	–0.002 (–0.01 to 0.006)	.59	–0.32 (–1.44 to 0.79)	.57	–0.22 (–0.75 to 0.32)	.41	–0.007 (–0.03 to 0.02)	.59
Antiestrogen therapy	–0.03 (–0.11 to 0.04)	.42	4.25 (–6.51 to 14.91)	.44	1.70 (–3.69 to 6.85)	.53	–0.22 (–0.48 to 0.05)	.11
Time: T2††	0.12 (0.04 to 0.20)	.004	7.82 (–3.31 to 18.96)	.17	1.97 (–3.81 to 7.64)	.50	0.31 (0.02 to 0.61)	.04
Time: T3††	0.21 (0.13 to 0.29)	<.001	2.92 (–8.36 to 14.12)	.62	–4.90 (–10.71 to 0.94)	.10	–0.003 (–0.31 to 0.30)	.98
Group: nonchemo patients‡‡	0.10 (–0.05 to 0.24)	.20	–15.79 (–37.02 to 5.16)	.14	–3.43 (–11.73 to 4.92)	.42	0.50 (0.10 to 0.89)	.01
Group: chemo patients‡‡	–0.04 (–0.18 to 0.11)	.61	0.72 (–20.00 to 20.46)	.94	4.41 (–3.89 to 12.33)	.28	0.72 (0.34 to 1.11)	<.001
Interactions of time and group								
T2 x nonchemo patients	–0.04 (–0.17 to 0.09)	.54	2.00 (–15.71 to 19.57)	.82	0.01 (–9.01 to 9.05)	.99	–0.24 (–0.71 to 0.21)	.30
T2 x chemo patients	–0.04 (–0.15 to 0.08)	.52	11.82 (–3.82 to 27.50)	.15	–0.90 (–9.11 to 7.08)	.83	–0.54 (–0.97 to –0.12)	.01
T3 x nonchemo patients	–0.13 (–0.26 to –0.005)	.04	9.71 (–8.30 to 27.50)	.29	8.01 (–0.82 to 16.66)	.08	–0.11 (–0.58 to 0.35)	.64
T3 x chemo patients	–0.13 (–0.25 to –0.003)	.04	18.86 (1.75 to 36.19)	.03	6.46 (–2.30 to 15.07)	.15	0.003 (–0.45 to 0.45)	.99

*Units are z-values; higher values indicate better functioning. CI = bootstrapped confidence interval (10 000 repetitions); IQ = intelligence quotient; PTSD = post-traumatic stress disorder; RT = reaction time; T1 = baseline assessment, before the start of therapy for patients; T2 = assessment after completion of chemotherapy or at matched intervals; T3 = assessment approximately one year after baseline.

†Units are milliseconds; higher values indicate worse functioning.

‡Units are errors; higher values indicate worse functioning.

§Centered to the mean of the sample.

‖Square of the centered age variable.

¶Reference group: low educational level.

#Reference: premenopausal status.

**Centered to the mean of the control group.

††Reference: T1.

‡‡Reference group: control group.

Table 6. Associations of PTSD symptoms with performance and change on cognitive indices that showed effects of participant group one year after diagnosis

	All participants (n = 206)		Patients only (n = 150)	
Cognitive outcome at T3*	PTSD symptoms at T2	PTSD symptoms at T3	PTSD symptoms at T2	PTSD symptoms at T3
Composite cognitive performance				
correlation coefficient	–0.08	–0.12	–0.04	–0.11
P†	.11	.02‡	.49	.07
n	206	206	150	150
Composite cognitive change score				
correlation coefficient	–0.16	–0.17	–0.15	–0.17
P†	.002‡	.001‡	.009‡	.004‡
n	206	206	150	150
Alertness, RT condition 1				
correlation coefficient	0.06	0.02	0.09	0.03
P†	.26	.68	.11	.58
n	204	204	149	149
Alertness, RT condition 1, change score				
correlation coefficient	–0.06	–0.08	–0.04	–0.09
P†	.27	.12	.46	.15
n	203	203	148	148
Go/Nogo errors				
correlation coefficient	–0.15	–0.13	–0.17	–0.15
P†	.004‡	.01‡	.005‡	.02‡
n	202	202	147	147
Go/Nogo errors, change score				
correlation coefficient	–0.09	–0.03	–0.15	–0.06
P†	.08	.58	.01‡	.36
n	201	201	146	146

*All cognitive scores are z-standardized and corrected for age and education. RT = reaction time; T2 = assessment after completion of chemotherapy or at matched intervals; T3 = assessment approximately one year after baseline.
†Two-sided Kendall's tau test was used.
‡Statistically significant.

and lost statistical significance (B = 0.37, *P* = .16, n = 193) when the mediating effect of PTSD symptoms (bias-corrected bootstrap results for indirect effect: B = 0.15, 95% CI = 0.02 to 0.38) was accounted for (Figure 3).

To ensure that the observed mediation was not incidental to the fact that cancer patients had more opportunities to endorse PTSD symptoms—those related to the worst noncancer event as well as those related to cancer, whereas the latter opportunity did not exist for control subjects—the mediation model was additionally run with either cancer-related or non-cancer-related PTSD symptoms, whichever number was higher in an individual participant, as a mediator. The results changed only marginally (bias-corrected bootstrap results for indirect effect: B = 0.17, 95% CI = 0.02 to 0.42).

Discussion

In the Cognicares study, we investigated whether any differences of cognitive performance and cognitive change between breast cancer patients who did or did not receive chemotherapy and healthy control subjects were mediated by cancer-related post-traumatic stress. Only very limited cognitive dysfunction was observed. Neither of the two patient groups showed a statistically significantly elevated rate of individual cognitive impairment at any time point, and similar performance of patients and control subjects was found on most indices of specific cognitive abilities, with two exceptions: Both patient groups performed consistently worse than the control subjects on a computerized measure of behavioral control, Go/Nogo errors, notwithstanding some intermittent improvement of the chemotherapy patients. In contrast, only patients who had received chemotherapy showed decline of reaction time on a computerized test of alertness at one year.

When cognitive indices were aggregated in a composite score of overall cognitive functioning, thus allowing small differences to add up, decline of both patient groups relative to control subjects emerged at one year after diagnosis, whereas steady improvement was observed in the sample as a whole. Apparently, the patients had benefitted less from practice on the neuropsychological tests than the control subjects. Overall cognitive performance was statistically significantly associated with one of two self-report measures of cognitive functioning at one year.

Two of the three cognitive measures that showed effects of participant group, composite cognitive change and Go/Nogo errors, were statistically significantly associated with PTSD symptoms at one year. The hypothesized mediation effect of post-traumatic stress could be demonstrated for only one of these indices: As observed prior to treatment (13), the effect of having cancer on Go/Nogo errors was mediated by PTSD symptoms also one year after diagnosis.

Our finding of cognitive dysfunction irrespective of chemotherapy is in line with a recently published meta-analysis (75) and a study in patients with colorectal cancer, the largest investigation of cancer-related cognitive dysfunction to date (27). In our study, the only decline limited to chemotherapy patients was found on a test of alertness that required pressing a mouse

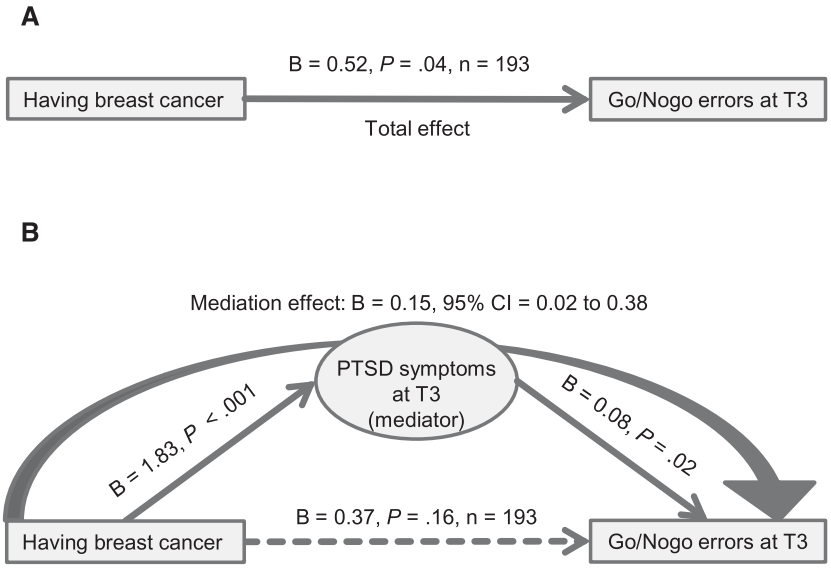

Figure 3. Mediation of the effect of having breast cancer on Go/Nogo errors by current post-traumatic stress disorder (PTSD) symptoms one year after diagnosis. **A)** Having breast cancer increases Go/Nogo errors at T3 by a mean of 0.52 errors (total effect). **B)** The mediation effect of PTSD symptoms increases Go/Nogo errors at T3 by a mean of 0.15 errors; having cancer increases PTSD symptoms at T3 by a mean of 1.83 symptoms; each PTSD symptom at T3 increases Go/Nogo errors at T3 by a mean of 0.08 errors. If mediation is accounted for, the remaining effect of having cancer on Go/Nogo errors at T3 (**dotted line**) is not statistically significant ($P = .16$). The following covariates were included: depression score at T3 (B = –0.02, $P = .37$); age (B = -0.15, $P = .05$); age squared (B = 0.002, $P = .05$); menopausal status at T3 (B = 0.24, $P = .34$); antiestrogen therapy at T3 (B = –0.17, $P = .44$); dummy coded educational level with low level as reference category (medium level: B = 0.17, $P = .49$; high level: B = 0.13, $P = .67$; university degree: B = 0.14, $P = .61$); estimated premorbid intelligence (B = 0.0008, $P = .90$); medication potentially affecting brain function at T3 (B = –0.003, $P = .99$). Statistical significance of the estimated regression coefficients was tested with a *t* statistic, controlling for all covariates in the model. The mediation effect was tested with a nonparametric bootstrapping procedure (10 000 repetitions). All statistical tests were two-sided. B = unstandardized regression coefficient, units are errors on the Go/Nogo test; CI = bootstrapped 95% confidence interval; T3 = assessment approximately one year after baseline.

button whenever a cross appeared on a monitor. Specific impairment of psychomotor speed after chemotherapy has previously been observed (76) and may at least partly be due to peripheral neuropathy (77). Furthermore, no deleterious effects of antiestrogen therapy were observed.

Our findings suggest that the psychological consequences of cancer may contribute more importantly to cognitive dysfunction than side effects of medication. Whereas the effect of narrowly defined post-traumatic stress does not fully explain breast cancer–related cognitive dysfunction, it may be part of a concert of factors like insomnia, fatigue, psychological morbidity, and prolonged sick leave, all of which ensue from the psychological burden and life disruption associated with cancer. This assumption is compatible with previous observations of little (78) or no (79–81) cognitive dysfunction particularly in European breast cancer patients. Relatively high standards of social security may shield these patients from cancer-related stress to some extent; and PTSD is altogether less endemic in several European countries, including Germany, than in the United States and many other regions (82).

We found more pronounced cognitive dysfunction at one year than at seven months after diagnosis. Late-onset cognitive impairment has previously been reported (83) and may be caused by effects of chronic stress that fully unfold only over time (84).

Strengths of the Cognicares study include a large sample, low attrition, a neuropsychological battery composed of paper-and-pencil and computerized tests, and clinical diagnostics of PTSD symptoms. To safeguard against spurious results, self-selection of participants—particularly of control subjects—was avoided to minimize selection bias (85), and outliers, nonlinear relationships, and multiple testing were addressed in the analyses.

Even though to the best of our knowledge cognitive function has never before been longitudinally tested in as many newly diagnosed young and middle-aged breast cancer patients as in the Cognicares study, sample size is still a limitation. An FDR of 20%, which permits one of five statistically significant results to be false positive, was chosen to balance the risk of false-positive and false-negative results. We can therefore not exclude that part of the observed differences of cognitive performance between patients and control subjects is a chance finding. Furthermore, nonexhaustive assessment of non-cancer-related PTSD symptoms in breast cancer patients and control subjects alike may have led to some degree of inaccuracy.

The Cognicares study found evidence of subtle cognitive dysfunction in breast cancer patients that seems largely independent of chemotherapy. The effect of cancer-related post-traumatic stress on specific cognitive abilities that was observed at our pretreatment evaluation (13) was found again one year after diagnosis. These findings suggest that post-traumatic stress is one of several factors other than treatment side effects that affect cognitive function in cancer patients. These factors remain to be investigated in studies that are large and methodologically sound enough to capture subtle effects.

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