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## Cognitive change in breast cancer patients up to 2 years after diagnosis

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**Abstract**

**Background:** Using the large nationwide CANTO cohort, we assessed cognitive functioning change after cancer treatments in a subgroup of breast cancer patients.

**Methods:** We included patients with newly diagnosed invasive stage I-III breast cancer enrolled in the CANTO sub-study focused on cognitive evaluation and healthy control women matched for age and education. Episodic and working memory, executive functions, processing speed, attention, self-report cognitive difficulties (SRCD), fatigue, anxiety/depression were assessed with neuropsychological tests and self-report questionnaires, before treatment (baseline), about 1 (year-1) and 2 years (year-2) after diagnosis. We used linear mixed models to study changes in cognition and tested the effect of adjuvant chemotherapy.

**Results:** We studied 276 localized breast cancer patients (62% chemotherapy (CT+)) compared to 135 healthy controls. After adjustment, patients had lower baseline working memory, processing speed and attention scores than healthy controls ( $p \leq 0.001$ ), and the difference remained significant over follow-up for working memory and processing speed. Executive function scores were similar between groups at baseline but decreased at year-1 among patients compared to healthy controls ( $p$  for change=0.006). This decrease in CT+ patients was significant when compared to healthy controls scores ( $p$  for change $<0.001$ ). After adjustment, SRCD were similar between breast cancer patients and healthy controls at baseline but increased in patients after treatment at year-1 ( $p$  for change=0.002).

**Conclusions:** Cognitive difficulties are an important concern in breast cancer patients, starting at diagnosis. Cancer treatments induce executive function decline and SRCD, which decrease over follow-up.

**Key-words:** Cognition, Breast cancer, Cancer treatments, Cohort study

**Abbreviations:**

**BC:** Breast cancer

**CRCI:** Cancer-related cognitive impairment

**CT:** Chemotherapy

**FACT-Cog:** Functional Assessment of Cancer Therapy-Cognitive Function

**HC:** Healthy controls

**PCI:** Perceived Cognitive Impairment

**SRCD:** Self-Report Cognitive Difficulties

## Introduction

Cancer-related cognitive impairment (CRCI), which is mainly studied after adjuvant chemotherapy in breast cancer (BC) patients (1–3), is one of the most frequent (40-75% of patients) side-effects reported by them (4–6). They report memory, concentration, multitasking and word-finding difficulties (7) and can be reported by several years after treatment, with a negative impact on their quality of life (8,9). Such cognitive difficulties are subtle or moderate and occur in 15 to 25% of BC patients after chemotherapy (1). However, according a recent systematic review, these difficulties may even appear during the course of cancer disease rather than after chemotherapy (10). Furthermore, they may occur before adjuvant treatment (11–14) and even before any cancer treatment, including BC surgery (15).

Although these difficulties are subtle and transient in most patients and seem to resolve within 6-12 months after cancer treatment (16,17), cross-sectional studies have shown that some BC patients have persistent impairment even 10 to 20 years after chemotherapy (18,19). However, few studies included a baseline assessment before any treatment and a follow-up of more than 12 months after cancer treatments, including both objective and subjective cognitive data in a large sample to assess the real long-term persistence of CRCI (10).

The present study used a subgroup of BC patients from the French, national, multicenter, prospective cancer and toxicities (CANTO) cohort (20,21) to describe cognitive functioning changes (objective scores and self-report cognitive difficulties (SRCD)) up to 2 years after diagnosis. We investigated the impact on cognition of (1) cancer, by comparing performances and SRCD of BC patients and those of healthy controls (HC); (2) chemotherapy, by comparing performances and SRCD of BC patients treated by chemotherapy (CT+) with those not treated by it (CT-).

## **Methods**

### Participants

This study is a sub-study of the nationwide French CANTO cohort of stage I-III BC patients (21) (trial registration: NCT01993498) which investigated cognitive functioning. Mainly BC patients were included before any treatment. A group of age-matched HC women from the general population, without cancer history (except basal cell cancer and in situ cancer of the cervix) and psychotropic medications was also recruited with local advertisements (newspapers, radios, flyers in Cancer Center) with the same eligibility criteria except cancer history. All recruitment details have been previously published (15). All participants provided written informed consent.

### Data collection

Patients' cognitive functioning was assessed at diagnosis before treatment (baseline), about 1 year after diagnosis (3-6 months after treatment completion; Year-1) and 2 years after diagnosis (Year-2), through a battery of neuropsychological tests administered by a graduate neuropsychologist.

To facilitate interpretation of the results and for the sake of clarity, test results are presented by cognitive domain. Five cognitive domains were assessed: episodic memory, working memory, information processing speed, attention, and executive function (Supplementary Table 1). Results were also presented by overall cognitive functioning. HC were assessed at the same time intervals as patients. SRCD, anxiety, depression and fatigue were also assessed at each visit by validated questionnaires: FACT-Cog, HADS and FA-12, respectively (15).

Clinical data were collected from medical records or during face-to-face health examinations and included the Charlson comorbidity index, main previous medical history, psychotropic medications, body mass index, cancer stage, HER2 status, cancer treatments (surgery,

chemotherapy regimen, radiotherapy, endocrine therapy, targeted therapies), time of treatment completion, toxicities and psychologist and neurologist consultations.

### Main outcomes

Raw neuropsychological test results at follow-up visits were corrected for practice effects (PE) as follows (22). First, PE were estimated for each test in HC by means of linear mixed models using discrete time and adjusting for baseline age, level of education, the number of previous completed assessments, and the time interval between consecutive assessments. By assuming the same PE patterns in patients as in HC, models were then used to predict PE in BC patients. Finally, PE-corrected scores were computed at each follow-up time in both patients and HC by subtracting cumulative PE predictions (i.e., the sum of PE up to the follow-up time) from raw scores. The newly computed scores were standardized to  $z$ -scores using the means and standard deviations of HC. Five cognitive domain scores were computed by averaging the corresponding  $z$ -scores (15). Cognitive domain impairment was defined by:  $z$ -score  $\leq -1.5$  below HC on two or more constitutive tests, or  $z$ -score  $\leq -2.0$  below HC on a single test, according to International Cognition and Cancer Task Force (ICCTF) recommendations (23). Overall objective cognitive impairment was defined by at least two impaired cognitive domains (24).

SRCD were primarily assessed by the Perceived Cognitive Impairment (PCI) subscale of the FACT-Cog, with higher scores indicating better perceived cognition. Clinically significant PCI complaints were defined as scoring lower than age-specific normative cut-offs for the FACT-Cog  $\leq 10^{\text{th}}$  percentile (25). Clinically significant symptoms of fatigue, anxiety, and depression were operationally defined as ratings FA-12 score  $\geq 40$  (26) and HADS score  $\geq 11$  (27).

### Statistical analysis

Baseline characteristics were compared between BC patients and HC and between patients CT+ and CT- by Student tests for continuous variables and Chi-square tests for categorical variables. Cognitive scores and PROs were described by group at each time point using means and standard deviations and percentages of impairment.

We used linear mixed models to compare cognitive changes over time between groups. Models included an intercept representing the average cognitive score at baseline, a discrete time variable representing average cognitive changes over time, group and group-by-time interaction effects allowing for group differences in baseline cognition and cognitive change respectively, and a random intercept accounting for within-subject correlation in repeated cognitive measures. We first assessed the effect of cancer on cognition by comparing BC patients and HC. Then, we assessed the effect of chemotherapy by distinguishing CT+ from CT- patients. The multivariable model was adjusted for baseline age, number of years of education, neurologic/psychiatric previous history (yes vs no), concomitant anxiety ( $\geq 11$ ) and concomitant cognitive fatigue ( $\geq 40$ ) (anxiety/fatigue at the same time points that cognitive data). In sensitivity analyses conducted among patients only, we further controlled the model for psychotropic medications (yes vs no) cancer stage (0-1 vs  $\geq 2$ ) and treatments including endocrine therapy and Herceptin (yes vs no). Six separate models were computed for the five objective cognitive domains and for SRCD. Given that for each model (viewed as separate hypotheses), 6 main tests were performed (2 comparisons BC vs HC and CT+ vs CT-, at 3 time-points), the significance threshold was corrected for multiple testing using the Bonferroni method ( $0.05/6$  independent tests = 0.008).

Missing covariates at follow-up (anxiety [6 missing at year-1] and cognitive fatigue [9 and 32 missing at year-1 and year-2]) were imputed by previous assessment scores. No baseline covariate had missing data, except cancer stage that was missing for two CT+ patients and

was thus imputed by the most frequent stage among CT+ patients. Statistical analyses were performed using R software version 4.1.0 and package lme4 version 1.1-27.1.

## **Results**

### Demographic and clinical characteristics

The baseline sample consisted of 296 BC patients whom 276 had undergone at least one neuropsychological assessment after baseline and were included in the present longitudinal analysis (Figure 1). Most of the patients (85%, n=235) had a baseline cognitive assessment after BC surgery. Furthermore, 172 (62%) BC patients had received CT (group CT+) and 104 (38%) had not (group CT-). The baseline sample also consisted of 149 age-matched HC women, including 135 who had undergone at least one assessment after baseline. Patients and controls were followed-up for a median of 24 months (interquartile range: 22-26).

Mean patients' age was 54±11 years at baseline, with CT+ patients being younger than CT- patients (Table 1). Fifty-five percent of patients had stage  $\geq$ II BC, 62% were treated with CT, 94% with radiation therapy, 83% with endocrine therapy and 12% with Herceptin. CT was mostly adjuvant (79%) and using a combination of anthracyclines and taxanes (>95%).

### Baseline cognitive and PRO measures

At baseline, cognitive domain scores were not significantly different between BC patients who underwent cognitive assessment before BC surgery and those after it. At baseline, 30% of BC patients had overall cognitive impairment compared to 15% of HC (Figure 2). Cognitive impairment was more frequent in BC patients than in HC in all cognitive domains except for executive function and episodic memory (Table 2 and Figure 2). SRCD (FACT-Cog PCI) were more frequently reported by BC patients than by HC (24 vs. 12%, Table 2). Anxiety symptoms and cognitive fatigue (FA-12) were also more frequent in BC patients than

in HC (31 vs. 12%, and 13 vs. 4%, respectively), but not depressive symptoms (5 vs. 1%, respectively, Table 2).

There was no significant difference in cognitive domains or SRCD between the two patient groups (CT+ vs. CT-), nor in any symptoms of anxiety, depression and fatigue (Table 3).

#### Cognitive and PRO measures at year-1 and year-2

Overall cognitive impairment was present in 33% of patients at year-1 and in 29% at year-2 (vs. 11% and 10% in HC at each time, respectively) (Figure 2). At all times, processing speed was the most impaired cognitive domain.

SRCD (FACT-Cog PCI) were reported significantly more frequently by BC patients than by HC at year-1 (36 vs. 13%) and year-2 (28 vs. 13%, Table 2). At year-1 and year-2, anxiety and depressive symptoms were comparable between patients and HC. Anxiety symptoms decreased between baseline and year-1 in BC patients. They also reported more severe cognitive fatigue (FA-12) than HC at year-1 (16 vs. 2%) but not at year-2 (10 vs. 7%, Table 2).

According to chemotherapy treatment, CT+ patients reported more SRCD than CT- patients at year-1 (43% vs. 24%) but not at year-2 (31% vs. 22%), and more severe cognitive fatigue at year-1 (21% vs 9%) but not at year-2 (11% vs. 9%) (Table 3). Median proportion of overlap in abnormal values from year-to-year was 54% (IQR=47- 60%, supplementary table 2).

#### Cognitive changes from baseline to follow-up

After adjustment, patients had lower working memory, processing speed and attention scores than HC at baseline (all  $p \leq 0.001$ , Table 4 and Figure 3), and the difference remained significant over follow-up for working memory and processing speed. Executive function

scores were similar between the groups at baseline but decreased at year-1 in patients compared to HC ( $p$  for change=0.006). This difference was no longer observed at year-2. There was no difference in episodic memory between the groups at any time.

When distinguishing patients by cancer treatments, CT+ patients had lower scores in processing speed than CT- patients at baseline ( $p=0.003$ ) but not at follow-up (Table 5). Baseline executive function was comparable between the patient groups, but scores decreased over time in CT+ compared to CT- patients ( $p$  for change at year1 = 0.03;  $p$  for change at year 2 < 0.01; Table 5), though this decrease did not reach the Bonferroni corrected significance threshold. Similar findings were observed when further adjusting for psychotropic medications, cancer stage and treatment (Supplementary Table 3). Of note, this decrease in CT+ patients' executive function from baseline to post-treatment was significant when compared to HC scores ( $p$  for change=0.001; Table 5). No difference was found in z-scores on the other cognitive domains between CT+ and CT- patients.

After adjustment, SRCD were similar between BC patients and HC at baseline but increased in patients after treatment at year-1 ( $p$  for change=0.003, Table 4 and Figure 3), leading to a -4.6 point-difference on the FACT-Cog PCI at year-1 between BC patients and HC ( $p<0.001$ ). This difference was also observed at year-2 but was smaller and did not reach the Bonferroni corrected significance threshold ( $p<0.02$ ).

In particular, SRCD of CT+ patients, but not CT- patients, increased significantly from baseline to 1-year post-treatment compared to HC ( $p$  for change<0.001), with a difference of -5.2 points on the FACT-Cog PCI ( $p=0.001$ ). There was a slight difference in change in SRCD after treatment between CT+ and CT- patients in the univariate model ( $p$  for change = 0.003; Supplementary Table 3 and Supplementary Figure 1), but this difference disappeared after adjustment for confounders, especially cognitive fatigue and cancer stage (data not shown).

### Factors associated with cognitive outcomes

Important significant factors associated with cognitive domain scores in BC patients included age and education level (Supplementary Table 4). Important significant factors associated with SRCD included psychotropic medications, cognitive fatigue and anxiety (Supplementary Table 4). Endocrine or Herceptin therapies were not associated with cognitive domains or SRCD .

### **Discussion**

Using a large nationwide cohort, well-validated measures of SRCD and ICCTF-recommended cognitive tests, this study shows that cognitive difficulties are an important concern in BC patients that start at diagnosis and persist over two years. These difficulties mainly concern working memory and processing speed. Our results also suggest that cancer treatments induce executive function decline and SRCD within the first year, with improvement two years after diagnosis.

Thirty percent of BC patients had objective cognitive impairment before cancer treatment. After adjustment, our patients had lower baseline working memory, processing speed and attention scores at diagnosis than HC.

After cancer treatments, these differences between BC patients and HC also remained significant for working memory and processing speed over follow-up, up to 2 years after diagnosis. Thus, cognitive difficulties are an important concern in BC patients, starting at diagnosis and persisting for at least two years after diagnosis independently of treatment received.

Furthermore, one year post-diagnosis (3-6 months after treatment completion), we found that cancer treatments had induced executive functioning decline, likely due to chemotherapy. According to a recent meta-analysis (28), executive function is one of the two main domains impacted by chemotherapy 6 months or more after the course of treatment. On the other hand, attention, the second domain mainly impacted by chemotherapy, had not declined, maybe due in part to the heterogeneity of the tests used to assess it.

Our results are in line with those of Janelsins et al. (29) who found that CT+ BC patients experienced decline in executive functions after CT compared to HC. However, they did not include CT- BC patients, so they could not draw conclusions about the putative effect of CT. In our study, although only CT+ patients but not CT- patients demonstrated significant decline in executive function compared to HC, we did not find a significant difference of change in executive function between CT+ and CT- patients. Further studies are needed to clarify whether CT contributes to post-treatment cognitive impairment.

Memory decline was also observed in the study by Janelsins et al., but not in ours, a discrepancy perhaps due to methodological differences. They presented their results in terms of cognitive test scores and observed a cognitive decline on only 4/8 memory test scores, while we were more restrictive by presenting cognitive domains, including two memory domains in which there was no significant post-treatment decline.

In addition to reporting objective cognitive outcomes, we reported SRCD, a dimension that considerably affects quality of life. The FACT-Cog questionnaire which specifically assesses cognition in cancer patients (30).

At diagnosis and follow-up, about twice as many BC patients reported significant cognitive complaints than HC. However, after adjustment, and as previously found (5,15), this difference was not significant at baseline, with a strong relationship between SRCD and psychological factors and fatigue. After cancer treatments, SRCD increased at year-1, and

decreased at year-2 post-diagnosis. Nevertheless, CT+ patients reported more SRCD at year-1 than CT- patients ((43 vs. 24%), although this difference was not significant after full adjustment on multiple cofounders (with a strong association with cognitive fatigue and cancer stage). A similar post-treatment increase in SRCD in BC patients compared to HC 7 months after CT was found by Janelins et al. (5). Our longer follow-up shows that the cognitive difficulties of CT+ BC patients seem to decrease 2 years after diagnosis.

Overall, if the proportion of patients with objective cognitive impairment remains stable across the different assessment (except for executive functions), the proportion of patients with SRCD increase after cancer treatment. This result could be partly explained by the fact that SRCD are strongly associated with fatigue (15), that increased at year-1, and could be more sensitive than objective cognitive scores to report changes. Indeed, compensatory mechanisms could allow patients to compensate some objective cognitive impairment and this is moreover reflected in an increase in SRCD (31).

As frequently found, important factors associated with cognitive domain scores included age and education level (32) and those associated with SRCD included psychotropic medications and psychological factors (cognitive fatigue and anxiety) (33–35), especially at baseline. However, endocrine and Herceptin therapies were not associated with cognition. Indeed, the impact of endocrine therapies on cognition has received little attention and results are inconsistent (36).

Limitations of this study include the lack of power of subgroup analysis comparing CT+ to CT- patients, especially when adjusting for confounders in sensitivity analyses and controlling for multiple comparisons. The first follow-up assessment was performed 3-6 months after treatment completion (year-1). The qualitative comments of many patients during the

neuropsychological study assessment and the findings of other studies (13,37,38) show that the cognitive impairment of some BC patients may partly of fully abate after one year. Our follow-up assessment may have been conducted too late to demonstrate any post-treatment cognitive impairment. Moreover, episodic memory assessment is based only on one cognitive test at the opposite of other cognitive domains. We did not use normative data and results are highly dependent on our control population.

Nevertheless, few large studies have assessed CRCI with a follow-up of more than 2 years after diagnosis in a well-controlled longitudinal study design including both objective and subjective measures. In addition, none of them included a sample of more than 100 patients in each group (CT+ or CT-) and an HC group. Furthermore, well-validated measures of SRCD and ICCTF-recommended cognitive tests were used. Test results were presented by cognitive domain in order to facilitate interpretation and for the sake of clarity. Finally, practice effects were controlled for and multivariable models were adjusted for several variables.

Cognitive difficulties are an important concern in BC patients from diagnosis. This large nationwide cohort study suggest that cancer treatments may induce executive function decline and SRCD, up to two years after diagnosis. These findings need to be confirming with larger studies. Furthermore, interventions should be developed in clinical practice to reduce CRCI and to manage BC patients during the first year of their treatment.

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Author contributions:

Conceptualization: ML, IHL, FA, CC, SD, FJ. Data Curation: ML, AC. Formal Analysis: SLA. Funding Acquisition: ML, FA, FJ. Investigation: ML, IHL, OR, JLF, BP, JP, CL, AC, CC, LM, FL, LV, MB, EB, MB, GB. Project Administration: ML, OQ, SE, SD, FJ. Resources: BG. Supervision: IVL. Writing - Original Draft: ML, SLA. Writing - Review & Editing: IHL, IVL, FJ.

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## Data Availability

Data were provided by CANTO cohort and will be shared on request to c-gaudin@unicancer.fr.

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**Table 1.** Characteristics of breast cancer patients and healthy controls of CANTO-Cog<sup>a</sup>.

Characteristics	Healthy controls (HC)	All breast cancer patients (BC)	$P_{BC\ vs\ HC}$	Cancer patients with CT (CT+)	Cancer patients without CT (CT-)	$P_{CT+\ vs\ CT-}$
Total No.	135	276		172	104	
<b>Demographic</b>						
Mean age (SD) [range], y	54 (9) [19-71]	54 (11) [28-83]	0.42	52 (11) [28-83]	59 (9) [42-81]	<.001
Age $\geq 65$ y, No. (%)	16 (12)	44 (16)	0.34	22 (13)	22 (21)	0.10
Education, mean years (SD) [range]	13.5 (2.7) [9.0-22.0]	13.1 (2.8) [5.0-24.0]	0.18	13.2 (2.7) [9.0-20.0]	12.9 (3.0) [5.0-24.0]	0.45
<b>Education level<sup>b</sup>, No. (%)</b>						
Low	7 (5)	23 (8)	0.25	14 (8)	9 (9)	0.57
Middle	59 (44)	133 (48)		79 (46)	54 (52)	
High	69 (51)	120 (43)		79 (46)	41 (39)	
<b>Clinical</b>						
<b>ECOG, No. (%)</b>						
0	--	254 (97)	--	162 (99)	92 (94)	0.02
missing		15		9	6	
<b>Co-morbidities</b>						
<b>Charlson index, No. (%)</b>						
0	--	202 (78)	--	123 (77)	79 (79)	0.81
$\geq 1$		58 (22)		37 (23)	21 (21)	
missing		16		12	4	
Previous pulmonary history, No. (%)	5 (4)	42 (16)	0.04	21 (12)	21 (21)	0.09
Previous gynaecologic history, No. (%)	29 (21)	162 (60)	0.04	99 (58)	64 (64)	0.42
Previous cardio-vascular history, No. (%)	11 (8)	70 (26)	<.001	43 (25)	27 (27)	0.87
Previous neurologic/psychiatric history, No. (%)	7 (5)	72 (26)	<.001	40 (23)	32 (31)	0.22
Psychotropic medications <sup>c</sup> , No. (%)	0 (0)	23 (8)	--	14 (8)	9 (9)	0.99
Mean BMI (SD), kg/m <sup>2</sup>	--	26.2 (5.2)	--	26.4 (5.4)	25.9 (4.8)	0.46
Postmenopausal, No. (%)	--	141 (52)	--	72 (42)	69 (68)	<.001
missing, No.		3		1	2	
Cancer stage $\geq$ II, No. (%)	--	151 (55)	--	132 (77)	19 (18)	<.001
missing, No.		2		2	0	
Grade I-II, No. (%)	--	186 (59)	--	89 (52)	97 (97)	<.001
missing, No.		4		0	4	
HER2-positive, No. (%)	--	34 (12)	--	32 (19)	2 (2)	<.001
Missing, No.		1		0	1	
Breast conserving surgery, No. (%)	--	206 (75)	--	113 (66)	93 (89)	<.001
Mastectomy, No. (%)		81 (29)		65 (38)	16 (15)	<.001
Sentinel lymph node biopsy, No. (%)	--	203 (74)	--	105 (61)	98 (94)	<.001
Lymph node dissection, No. (%)		110 (40)		102 (59)	8 (8)	<.001
CT, No. (%)	--	172 (62)	--	172 (100)	0 (0)	<.001
<b>Neo-adjuvant CT, No. (%)</b>						
Anthracyclines-taxanes (%)	--	--	--	36 (21)	--	--
No. of cycles (mean, SD; range)				3.9 (1.1) [3-6]		
<b>Adjuvant CT, No.</b>						
Anthracyclines-taxanes (%)	--	--	--	136 (79)	--	--
				127 (74)		
				2 (1)		

Anthracyclines-based (%)				7 (4)		
Taxanes-based (%)				3.7 (1.3) [3-8]		
Mean no. of cycles (SD) [range]						
Adjuvant radiotherapy, No. (%)	--	259 (94)	--	170 (99)	89 (86)	<.001
Adjuvant endocrine therapy, No.	--	228 (83)	--	134 (78)	94 (90)	0.001
Tamoxifen ± LHRH , No. (%)		76 (28)		54 (31)	22 (21)	
AI ± LHRH, No. (%)		113 (41)		56 (33)	57 (55)	
Tamoxifen -> AI ± LHRH, No. (%)		39 (14)		24 (14)	15 (14)	
Targeted therapies, No. (%)	--		--			
Herceptin		34 (12)		34 (20)	0 (0)	<.001
Others		6 (2)		5 (3)	1 (1)	0.52
Mean days since end of CT+/-RT at Year-1 (SD)	--	150 (52)	--	150 (48)	170 (58)	0.02
missing		5		3	2	
Toxicities at M0, No. (%)	--		--			
CTCAE grade ± 3 <sup>d</sup>		68 (25)		45 (26)	23 (22)	0.54
Mean pain (SD) over 10		5.6 (2.3)		5.7 (2.4)	5.5 (2.2)	0.45
Attention disorder		132 (48)		97 (56)	35 (34)	<.001

SD: standard deviation; PS: Performance Status; WHO: World Health Organization; BMI: Body Mass Index,

CT: chemotherapy

<sup>a</sup>% are of non-missing values<sup>b</sup> Education level, number of years of school: low: <10; middle: 10-12, high: >12

<sup>c</sup> Level 3 on the WHO analgesic ladder, anxiolytics, antidepressant treatments and hypnotics

<sup>d</sup> CTCAE grade ± 3 cardiovascular, gynecologic, rheumatological, GI, dermatological, pulmonary, or neurologic toxicity

**Table 2.** Cognitive measures and patient-reported outcomes (PROs) among breast cancer patients (BC) and matched healthy controls (HC) at baseline pre-treatment and at 1- and 2-year post-treatment initiation

Cognitive measures and PROs <sup>a</sup>	BC (n=276)				HC (n=135)							
	Baseline (n=276)		Year-1 (n=273)		Year-2 (n=247)		Baseline (n=135)		Year-1 (n=130)		Year-2 (n=119)	
	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal
Episodic Memory	-0.16 (0.84) <sup>b</sup>	19	-0.11 (0.79)	15	-0.05 (0.86)	14	0.04 (0.82)	11	0.03 (0.71)	8	0.04 (0.75)	8
Working Memory	-0.47 (0.73) <sup>d</sup>	18 <sup>c</sup>	-0.40 (0.80) <sup>d</sup>	17 <sup>b</sup>	-0.37 (0.83) <sup>d</sup>	20 <sup>d</sup>	0.04 (0.76)	7	0.04 (0.77)	8	0.06 (0.74)	3
Processing Speed	-0.37 (0.76) <sup>d</sup>	35 <sup>d</sup>	-0.43 (0.81) <sup>d</sup>	35 <sup>d</sup>	-0.35 (0.82) <sup>d</sup>	34 <sup>b</sup>	0.00 (0.64)	19	0.00 (0.62)	19	0.04 (0.59)	22
Attention	-0.37 (0.98) <sup>d</sup>	22 <sup>c</sup>	-0.24 (0.97) <sup>b</sup>	21 <sup>c</sup>	-0.24 (1.00) <sup>c</sup>	20 <sup>c</sup>	0.01 (0.77)	9	-0.01 (0.79)	8	0.02 (0.74)	8
Executive Function	-0.09 (0.58)	19	-0.23 (0.58) <sup>d</sup>	28 <sup>c</sup>	-0.11 (0.55) <sup>b</sup>	23	-0.01 (0.51)	17	-0.01 (0.44)	15	0.03 (0.48)	16
FACT-Cog												
PCI	58.0 (11.9) <sup>d</sup>	24 <sup>c</sup>	53.6 (13.9) <sup>d</sup>	36 <sup>d</sup>	55.6 (11.9) <sup>d</sup>	28 <sup>c</sup>	61.6 (8.6)	12	60.2 (8.5)	13	59.9 (9.3)	13
PCA	19.9 (5.4) <sup>c</sup>	16 <sup>b</sup>	18.0 (5.6) <sup>d</sup>	25 <sup>d</sup>	18.8 (5.0) <sup>d</sup>	18 <sup>b</sup>	21.4 (4.6)	8	20.9 (4.4)	3	21.2 (4.5)	9
QoL	11.7 (4.1) <sup>d</sup>	23 <sup>d</sup>	11.8 (4.3) <sup>d</sup>	23 <sup>d</sup>	12.7 (3.7) <sup>c</sup>	17 <sup>b</sup>	13.9 (3.1)	9	13.9 (3.3)	8	13.9 (3.4)	9
Oth	15.0 (2.1)	19	14.9 (2.0) <sup>d</sup>	23	15.1 (1.7)	20	15.3 (1.3)	16	15.4 (1.0)	17	15.3 (1.2)	21
HADS												
Anxiety	8.6 (4.4) <sup>d</sup>	31 <sup>d</sup>	6.8 (3.9)	16	6.9 (3.9)	19	6.5 (3.5)	12	6.6 (3.4)	13	6.6 (3.5)	16
Depression	3.8 (3.6) <sup>d</sup>	5	3.3 (3.0)	4	3.5 (3.0)	3	2.7 (2.3)	1	3.0 (2.7)	2	3.8 (3.1)	6
Fatigue												
Cognitive	16.5 (22.5) <sup>d</sup>	13 <sup>c</sup>	20.2 (25.3) <sup>d</sup>	16 <sup>d</sup>	16.7 (22.9) <sup>be</sup>	10 <sup>e</sup>	10.4 (16.1)	4	11.2 (13.7)	2	13.6 (18.4)	7
Physical	25.5 (23.8) <sup>b</sup>	27 <sup>b</sup>	32.6 (23.3) <sup>c</sup>	35 <sup>c</sup>	31.3 (23.7) <sup>be</sup>	31 <sup>e</sup>	20.9 (18.3)	16	26.4 (22.2)	21	26.2 (22.6)	25
Emotional	25.6 (27.9) <sup>d</sup>	25 <sup>c</sup>	20.4 (24.3) <sup>b</sup>	20 <sup>b</sup>	19.9 (25.0) <sup>e</sup>	17 <sup>e</sup>	13.1 (17.8)	11	15.7 (22.1)	12	16.7 (23.2)	15

<sup>a</sup> For patient-reported outcomes, mean (SD) and % are of non-missing values. There were less than 5% of missing values at each time for each group unless specified.

<sup>b</sup> p<0.05, <sup>c</sup> p<0.01, <sup>d</sup> p<0.001 for BC vs. HC comparison of scores (Student test) or proportions (Chi-squared test) at a given time point.

<sup>e</sup> 13% of BC patients assessed at Year-2 were missing cognitive, physical and emotional fatigue assessment.

**Table 3.** Cognitive measures and patient-reported outcomes (PROs) among breast cancer patients treated with chemotherapy (CT+) and without chemotherapy (CT-) at baseline and 1- and 2-year post-treatment initiation.

Cognitive measures and PROs <sup>a</sup>	CT+ (n=172)						CT- (n=104)					
	Baseline (n=172)		Year-1 (n=169)		Year-2 (n=156)		Baseline (n=104)		Year-1 (n=104)		Year-2 (n=91)	
	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal
<b>Cognitive domains</b>												
Episodic Memory	-0.15 (0.85)	19	-0.12 (0.85)	16	-0.04 (0.86)	15	-0.18 (0.81)	19	-0.11 (0.69)	12	-0.05 (0.87)	11
Working Memory	-0.53 (0.70)	19	-0.38 (0.75)	15	-0.31 (0.84)	16	-0.37 (0.76)	17	-0.43 (0.88)	20	-0.45 (0.81)	26
Processing Speed	-0.44 (0.75)	39	-0.40 (0.73)	34	-0.30 (0.83)	32	-0.26 (0.77)	30	-0.48 (0.93)	37	-0.44 (0.79)	39
Attention	-0.37 (0.98)	24	-0.24 (0.98)	22	-0.21 (0.98)	22	-0.37 (1.00)	20	-0.25 (0.96)	20	-0.29 (1.04)	17
Executive Function	-0.05 (0.55)	17	-0.24 (0.54)	28	-0.14 (0.56)	23	-0.15 (0.63)	22	-0.22 (0.65)	28	-0.07 (0.53)	22
<b>FACT-Cog</b>												
PCI	58.5 (12)	25	52.5 (15.1)	43 <sup>g</sup>	55.2 (12.7)	31	57.3 (11.7)	21	55.5 (11.6)	24	56.3 (10.4)	22
PCA	20.1 (5.7)	19	17.5 (6.0) <sup>f</sup>	34 <sup>h</sup>	18.6 (5.2)	23 <sup>f</sup>	19.4 (4.8)	12	19.0 (4.7)	12	19.1 (4.6)	10
QoL	11.5 (4.2)	24	11.4 (4.5) <sup>f</sup>	27	12.5 (3.9)	19	12.0 (4.0)	20	12.6 (3.8)	17	12.9 (3.2)	15
Oth	15.1 (2.0)	19	14.8 (2.2)	25	15.0 (1.9)	21	14.9 (2.3)	20	15.0 (1.7)	19	15.2 (1.4)	19
<b>HADS</b>												
Anxiety	8.5 (4.2)	31	6.6 (3.6)	16	6.8 (4.1)	19	8.7 (4.8)	30	7.1 (4.2)	17	7.0 (3.7)	20
Depression	3.8 (3.5)	4	3.4 (3.1)	4	3.4 (2.9)	3	3.7 (3.7)	6	3.3 (2.9)	4	3.7 (3.1)	3
<b>Fatigue</b>												
Cognitive	17.2 (23.1)	14	22.8 (27.3) <sup>bf</sup>	21 <sup>bf**</sup>	18.5 (24.3) <sup>c</sup>	11 <sup>e</sup>	15.5 (21.5) <sup>d</sup>	12 <sup>d</sup>	16.2 (21.5)	9	13.8 (20.0) <sup>d</sup>	9 <sup>e</sup>
Physical	25.4 (24.6)	27	34.2 (24.5) <sup>bf</sup>	37 <sup>b</sup>	31.9 (24.2) <sup>c</sup>	32 <sup>e</sup>	25.7 (22.5) <sup>d</sup>	27 <sup>d</sup>	30.2 (21.2)	32	30.4 (23.0) <sup>d</sup>	30 <sup>e</sup>
Emotional	26.4 (29.1)	27	21.8 (25.2) <sup>bf</sup>	22 <sup>b</sup>	20.2 (24.1) <sup>c</sup>	16 <sup>e</sup>	24.1 (26.0) <sup>d</sup>	22 <sup>d</sup>	18.3 (22.7)	17	19.2 (26.6) <sup>d</sup>	19 <sup>e</sup>

<sup>a</sup> Mean (SD) and % are of non-missing values. There were less than 5% of missing values at each time for each group unless specified.

<sup>b</sup> 5.6% of CT+ patients assessed at Year-1 were missing cognitive, physical and emotional fatigue assessment.

<sup>c</sup> 14% of CT+ patients assessed at Year-2 were missing cognitive, physical and emotional fatigue assessment.

<sup>d</sup> 5.8% of CT- patients assessed at Pre-treatment were missing cognitive, physical and emotional fatigue assessment.

<sup>e</sup> 11% of CT- patients assessed at Year-2 were missing cognitive, physical and emotional fatigue assessment.

<sup>f</sup>  $p < 0.05$ , <sup>g</sup>  $p < 0.01$ , <sup>h</sup>  $p < 0.001$  for CT+ vs. CT- comparison of scores (Student test) or proportions (Chi-squared test) at a given time point.

**Table 4.** Unadjusted and adjusted differences in cognitive functioning between 276 patients with breast cancer (BC) and 135 healthy controls (HC) from baseline to 1- and 2-year post-treatment initiation.

Cognitive functioning <sup>a</sup>	Baseline difference		Year-1 difference		Year-2 difference		Baseline to Year-1 change difference		Baseline to Year-2 change difference	
	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p
Episodic Memory										
Unadjusted	-0.20 (0.08)	0.02	-0.15 (0.09)	0.07	-0.10 (0.09)	0.25	0.05 (0.08)	0.59	0.10 (0.09)	0.27
Adjusted	-0.12 (0.09)	0.16	-0.08 (0.09)	0.36	-0.02 (0.09)	0.80	0.04 (0.09)	0.65	0.10 (0.09)	0.29
Working Memory										
Unadjusted	-0.51 (0.08)	<.001	-0.45 (0.08)	<.001	-0.42 (0.08)	<.001	0.07 (0.06)	0.26	0.10 (0.06)	0.11
Adjusted	-0.49 (0.08)	<.001	-0.39 (0.08)	<.001	-0.36 (0.08)	<.001	0.10 (0.06)	0.10	0.13 (0.06)	0.045
Processing Speed										
Unadjusted	-0.37 (0.08)	<.001	-0.42 (0.08)	<.001	-0.37 (0.08)	<.001	-0.05 (0.06)	0.38	-0.01 (0.06)	0.93
Adjusted	-0.33 (0.08)	<.001	-0.37 (0.08)	<.001	-0.32 (0.08)	<.001	-0.03 (0.07)	0.61	0.02 (0.07)	0.79
Attention										
Unadjusted	-0.38 (0.10)	<.001	-0.25 (0.10)	0.01	-0.25 (0.10)	0.01	0.13 (0.06)	0.02	0.13 (0.06)	0.03
Adjusted	-0.33 (0.10)	0.001	-0.18 (0.10)	0.05	-0.24 (0.10)	0.01	0.15 (0.06)	0.02	0.09 (0.06)	0.16
Executive Function										
Unadjusted	-0.08 (0.06)	0.17	-0.22 (0.06)	<.001	-0.11 (0.06)	0.06	-0.14 (0.05)	0.002	-0.03 (0.05)	0.49
Adjusted	-0.02 (0.06)	0.79	-0.15 (0.06)	0.007	-0.07 (0.06)	0.21	-0.14 (0.05)	0.006	-0.06 (0.05)	0.27
Self-report cognitive difficulties										
Unadjusted	-3.6 (1.2)	0.003	-6.7 (1.2)	<.001	-3.8 (1.3)	0.002	-3.1 (1.1)	0.005	-0.2 (1.1)	0.83
Adjusted	-1.2 (1.1)	0.29	-4.6 (1.1)	<.001	-2.8 (1.2)	0.02	-3.4 (1.1)	0.003	-1.6 (1.2)	0.17

<sup>a</sup>  $\beta$  estimates (Standard Errors) are from linear mixed models. Adjustment includes baseline age, level of education, neurological or psychiatric comorbidities, concomitant anxiety and concomitant cognitive fatigue and their interactions with time. For all cognitive measures, lower scores indicate poorer cognition.

**Table 5.** Differences in cognitive functioning between breast cancer patients treated with chemotherapy (CT+), without chemotherapy (CT-) and healthy controls (HC) from baseline to 1- and 2-year post-treatment initiation (N=411).

Cognitive functioning <sup>a</sup>	Baseline differences		Year-1 difference		Year-2 difference		Baseline to Year-1 change differences		Baseline to Year-2 change differences	
	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p
<b>Episodic Memory</b>										
CT+ vs CT-	-0.10 (0.10)	0.30	-0.10 (0.10)	0.33	-0.08 (0.10)	0.43	0.01 (0.10)	0.96	0.02 (0.11)	0.84
CT+ vs HC	-0.16 (0.09)	0.09	-0.12 (0.09)	0.22	-0.05 (0.10)	0.59	0.04 (0.10)	0.67	0.10 (0.10)	0.29
CT- vs HC	-0.05 (0.11)	0.62	-0.02 (0.11)	0.87	0.03 (0.11)	0.78	0.04 (0.11)	0.74	0.08 (0.11)	0.46
<b>Working Memory</b>										
CT+ vs CT-	-0.18 (0.10)	0.07	0.01 (0.10)	0.92	0.08 (0.10)	0.42	0.19 (0.07)	0.008	0.26 (0.07)	<.001
CT+ vs HC	-0.56 (0.09)	<.001	-0.38 (0.09)	<.001	-0.33 (0.09)	<.001	0.17 (0.07)	0.01	0.22 (0.07)	0.001
CT- vs HC	-0.37 (0.10)	<.001	-0.39 (0.10)	<.001	-0.41 (0.11)	<.001	-0.02 (0.08)	0.82	-0.04 (0.08)	0.62
<b>Processing Speed</b>										
CT+ vs CT-	-0.28 (0.09)	0.003	0.04 (0.09)	0.64	0.05 (0.10)	0.57	0.32 (0.07)	<.001	0.33 (0.08)	<.001
CT+ vs HC	-0.44 (0.09)	<.001	-0.35 (0.09)	<.001	-0.30 (0.09)	<.001	0.09 (0.07)	0.21	0.14 (0.07)	0.05
CT- vs HC	-0.16 (0.10)	0.12	-0.39 (0.10)	<.001	-0.35 (0.10)	<.001	-0.23 (0.08)	0.003	-0.19 (0.08)	0.02
<b>Attention</b>										
CT+ vs CT-	-0.13 (0.11)	0.24	-0.12 (0.11)	0.28	-0.07 (0.11)	0.57	0.01 (0.07)	0.89	0.07 (0.07)	0.36
CT+ vs HC	-0.38 (0.10)	<.001	-0.23 (0.10)	0.03	-0.27 (0.10)	0.01	0.15 (0.07)	0.03	0.11 (0.07)	0.10
CT- vs HC	-0.25 (0.12)	0.046	-0.11 (0.12)	0.37	-0.20 (0.12)	0.09	0.14 (0.08)	0.06	0.04 (0.08)	0.57
<b>Executive Function</b>										
CT+ vs CT-	-0.00 (0.07)	0.99	-0.12 (0.07)	0.06	-0.15 (0.07)	0.03	-0.12 (0.06)	0.03	-0.15 (0.06)	0.01
CT+ vs HC	-0.02 (0.06)	0.80	-0.20 (0.06)	0.001	-0.13 (0.06)	0.045	-0.18 (0.05)	0.001	-0.11 (0.05)	0.046
CT- vs HC	-0.02 (0.07)	0.83	-0.08 (0.07)	0.27	0.02 (0.07)	0.76	-0.06 (0.06)	0.31	0.04 (0.06)	0.54
<b>Self-report cognitive difficulties</b>										
CT+ vs CT-	0.9 (1.3)	0.52	-1.6 (1.3)	0.25	-1.4 (1.4)	0.31	-2.4 (1.3)	0.07	-2.3 (1.4)	0.10
CT+ vs HC	-0.9 (1.2)	0.47	-5.2 (1.3)	<.001	-3.3 (1.3)	0.01	-4.3 (1.2)	0.001	-2.4 (1.3)	0.06
CT- vs HC	-1.8 (1.4)	0.22	-3.7 (1.4)	0.01	-1.9 (1.5)	0.23	-1.9 (1.4)	0.17	-0.1 (1.4)	0.92

<sup>a</sup>  $\beta$  estimates (Standard Errors) are from linear mixed models on breast cancer patients and healthy controls. Adjustment includes baseline age, level of education, neurological or psychiatric comorbidities, concomitant anxiety and concomitant cognitive fatigue, and their interactions with time. For all cognitive measures, lower scores indicate poorer cognition.

**Figure legends:****Figure 1.** Flow chart**Figure 2.** Cognitive impairment in each cognitive domains and overall among breast cancer patients and matched healthy controls at baseline pre-treatment and at 1- and 2-year post-treatment initiation.**Figure 3.** Predicted cognitive measures of 276 patients with breast cancer (BC) and 135 healthy controls (HC) from baseline to 1- and 2-year post-treatment initiation. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  for BC vs HC comparison of scores estimates at a given time point. Estimates are from linear mixed models adjusted for baseline age, level of education, neurological or psychiatric comorbidities, concomitant anxiety and concomitant cognitive fatigue and their interactions with time. Curves are plotted for an average study participant profile (an individual aged 54y, with 13y of schooling, no previous history of neurologic/psychiatric condition, no cognitive fatigue nor anxiety). For all cognitive measures, lower scores indicate poorer cognition

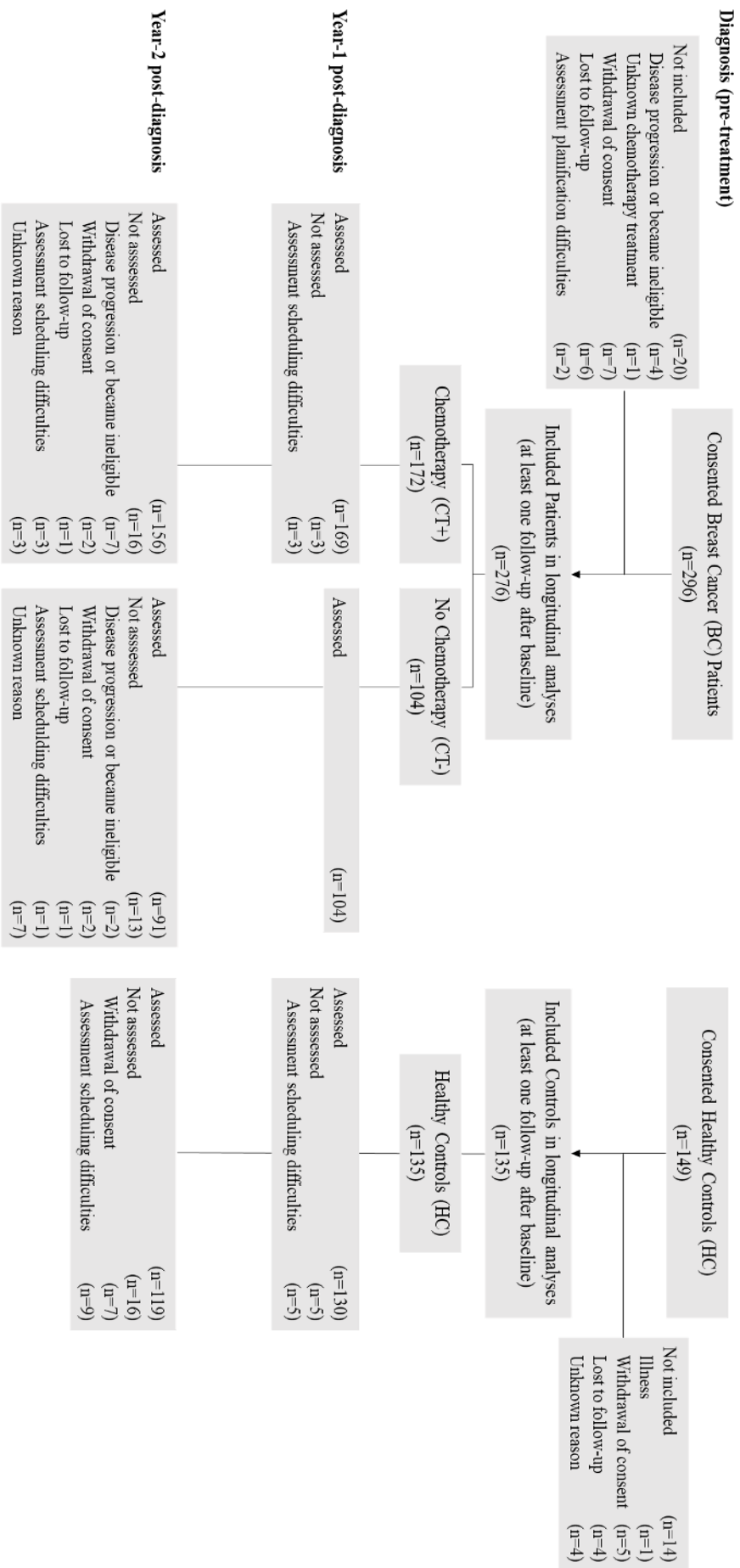
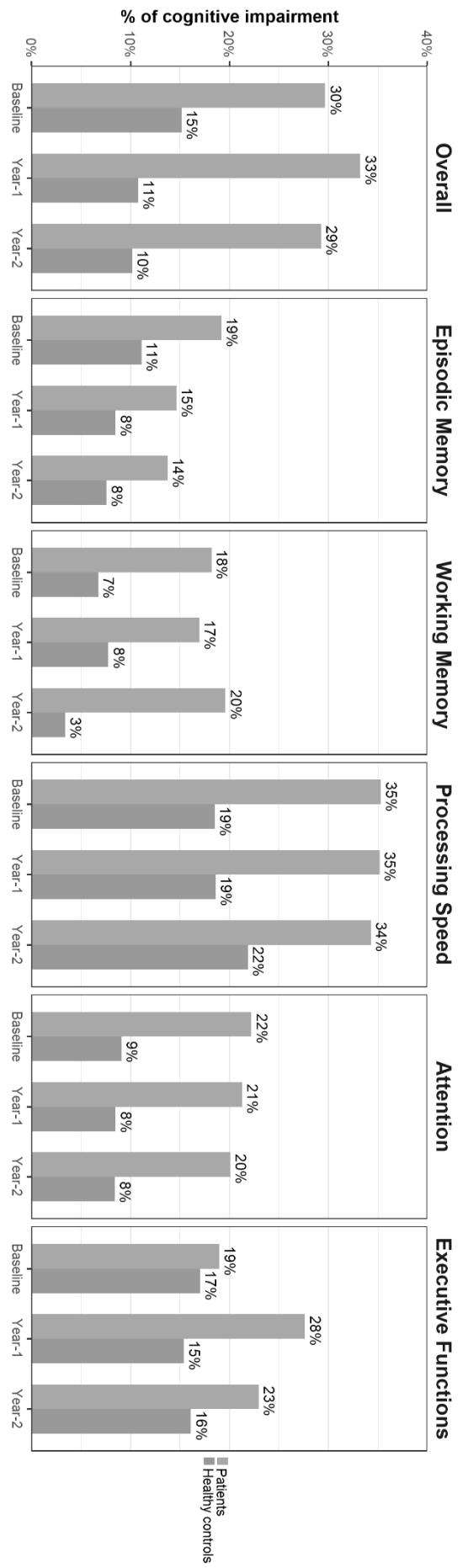
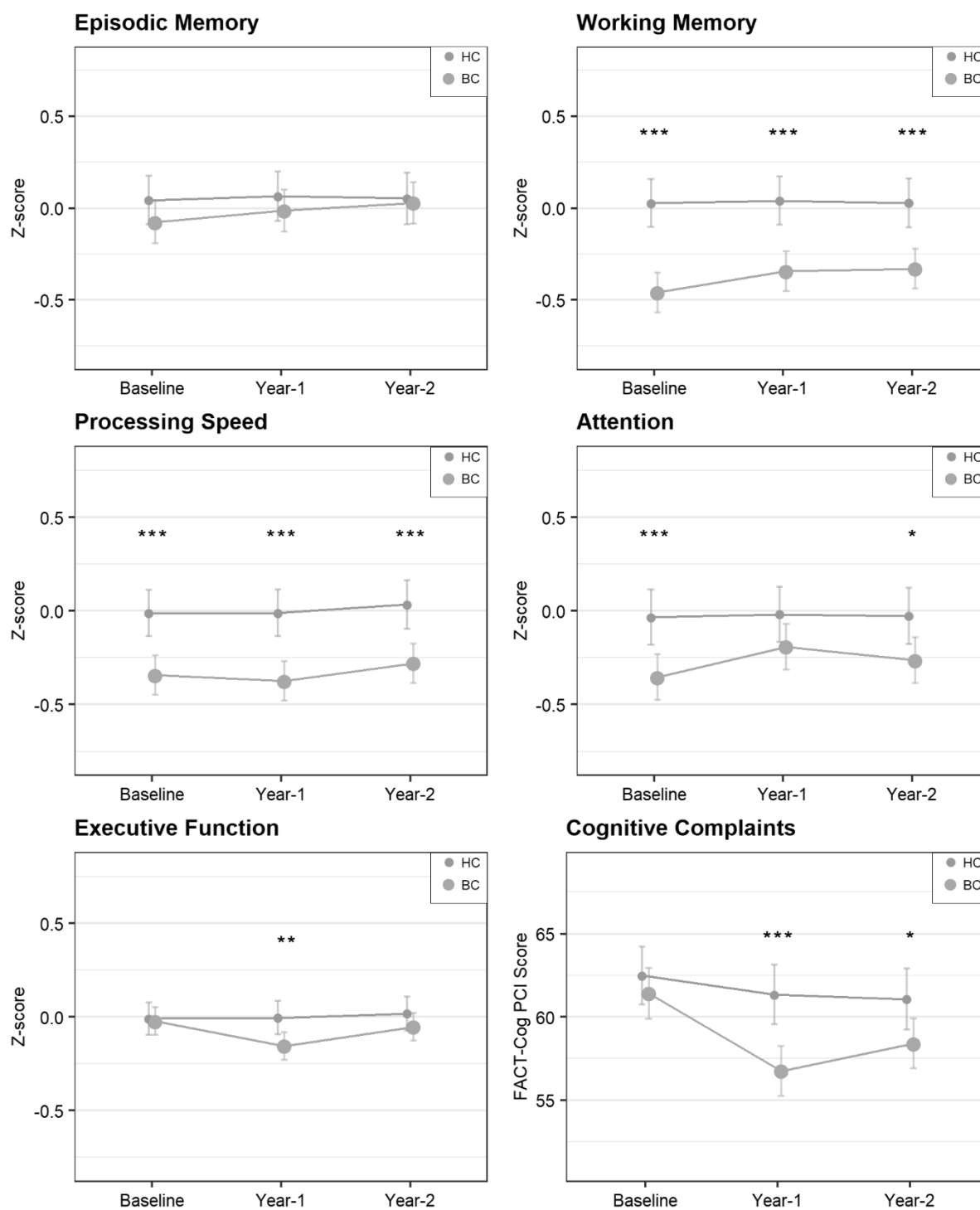


Figure 1.



**Figure 2.**

Figure 3.



## Supplementary Material

**Supplementary Table 1.** Cognitive domains and neuropsychological tests

Cognitive domain	Test	Outcome measure
Episodic memory		
Learning and memory	HVLT (39)	3 immediate free recall Free delayed recall
Working memory		
<i>Verbal modality</i>	WAIS-III (40): Digit-span WAIS-III (40): Letter-number sequencing	Scaled score, forward Scaled score, backward Scaled score
<i>Visual modality</i>	WMS-III: Spatial-span (41)	Scaled score, forward Scaled score, backward
Processing speed	TMT A (42)  Stroop (43)	Time to complete and errors  Time to complete color and word cards
Attention	WAIS-III (40): Symbol Search d2 test (44)	Scaled score % of errors (F%) Nb processed responses (GZ) Nb of correct responses (KL)
Executive function		
Flexibility	TMT B (42)	Time to complete and number of perseverative errors
Information generation	Verbal fluency: Category (animal) and Letter P (45)	Total score over 2 min
Inhibition	Stroop (43)	Time to complete and number of non-corrected errors: interference card – color card

HVLT: Hopkins Verbal Learning test; WMS: Wechsler Memory Scale; TMT: Trail Making Test

**Supplementary Table 2.** Proportion of abnormal cognitive and patient-reported outcomes at baseline, 1- and 2-year post-treatment initiation and proportion of overlap with previous assessment among breast cancer patients treated with chemotherapy (CT+) and without chemotherapy (CT-)

Cognitive measures and PROs <sup>a</sup>	CT+ (N=172)					CT- (N=104)								
	Baseline (N=172)		Year-1 (N=169)			Year-2 (N=156)		Baseline (N=104)		Year-1 (N=104)			Year-2 (N=91)	
	% abnormal		% abnormal	% overlap	% abnormal	% overlap	% abnormal	% abnormal	% overlap	% abnormal	% overlap			
<b>Cognitive domains</b>														
Episodic Memory	19%		16%	37%	15%	42%	19%	12%	54%	11%	30%			
Working Memory	19%		15%	52%	16%	54%	17%	20%	57%	26%	46%			
Processing Speed	39%		34%	54%	32%	51%	30%	37%	47%	39%	60%			
Attention	24%		22%	73%	22%	62%	20%	20%	60%	17%	73%			
Executive Function	17%		28%	35%	23%	56%	22%	28%	46%	22%	55%			
<b>FACT-Cog</b>														
PCI	25%		43% <sup>g</sup>	54%	31%	84%	21%	24%	52%	22%	60%			
PCA	19%		34% <sup>h</sup>	35%	23% <sup>f</sup>	72%	12%	12%	50%	10%	56%			
QoL	24%		27%	50%	19%	60%	20%	17%	41%	15%	50%			
Oth	19%		25%	38%	21%	56%	20%	19%	55%	19%	59%			
<b>HADS</b>														
Anxiety	31%		16%	64%	19%	40%	30%	17%	94%	20%	60%			
Depression	4%		4%	0%	3%	40%	6%	4%	25%	3%	67%			
<b>Fatigue</b>														
Cognitive	14%		21% <sup>bg</sup>	45%	11% <sup>c</sup>	80%	12% <sup>d</sup>	9%	22%	9% <sup>e</sup>	40%			
Physical	27%		37% <sup>b</sup>	55%	32% <sup>c</sup>	75%	27% <sup>d</sup>	32%	48%	30% <sup>e</sup>	77%			
Emotional	27%		22% <sup>b</sup>	55%	16% <sup>c</sup>	63%	22% <sup>d</sup>	17%	56%	19% <sup>e</sup>	50%			

<sup>a</sup> Mean (SD) and % are of non-missing values. There were less than 5% of missing values at each time for each group unless specified.

<sup>b</sup> 5.6% of CT+ patients assessed at Year-1 were missing cognitive, physical and emotional fatigue assessment.

<sup>c</sup> 14% of CT+ patients assessed at Year-2 were missing cognitive, physical and emotional fatigue assessment.

<sup>d</sup> 5.8% of CT- patients assessed at Pre-treatment were missing cognitive, physical and emotional fatigue assessment.

<sup>e</sup> 11% of CT- patients assessed at Year-2 were missing cognitive, physical and emotional fatigue assessment.

<sup>f</sup>p<0.05, <sup>g</sup>p<0.01, <sup>h</sup>p<0.001 for CT+ vs. CT- comparison of scores (Student test) or proportions (Chi-squared test) at a given time point.

**Supplementary Table 3.** Unadjusted and adjusted differences in cognitive functioning between breast cancer patients treated with chemotherapy (CT+) and without chemotherapy (CT-) from baseline to 1- and 2-year post-treatment initiation (N=276).

Cognitive measures and PROs <sup>a</sup>	Baseline difference		Year-1 difference		Year-2 difference		Baseline to Year-1 change difference		Baseline to Year-2 change difference	
	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p
	<hr/>									
Episodic Memory										
Unadjusted	0.04 (0.10)	0.73	-0.01 (0.10)	0.90	0.01 (0.11)	0.95	-0.05 (0.10)	0.63	-0.03 (0.10)	0.78
Adjusted	-0.11 (0.10)	0.30	-0.09 (0.10)	0.33	-0.08 (0.10)	0.44	0.01 (0.10)	0.96	0.02 (0.11)	0.83
Sensitivity	-0.19 (0.13)	0.13	-0.23 (0.13)	0.08	-0.11 (0.13)	0.42	-0.04 (0.13)	0.79	0.09 (0.14)	0.52
Working Memory										
Unadjusted	-0.15 (0.10)	0.12	0.05 (0.10)	0.60	0.14 (0.10)	0.16	0.20 (0.07)	0.004	0.29 (0.07)	<.001
Adjusted	-0.18 (0.10)	0.07	0.01 (0.10)	0.92	0.08 (0.10)	0.42	0.19 (0.07)	0.008	0.26 (0.07)	0.002
Sensitivity	-0.34 (0.13)	0.007	-0.08 (0.13)	0.55	0.02 (0.13)	0.88	0.26 (0.09)	0.005	0.35 (0.10)	<.001
Processing Speed										
Unadjusted	-0.18 (0.10)	0.07	0.09 (0.10)	0.39	0.12 (0.10)	0.24	0.27 (0.08)	<.001	0.30 (0.08)	<.001
Adjusted	-0.28 (0.09)	0.003	0.04 (0.09)	0.64	0.06 (0.10)	0.57	0.32 (0.07)	<.001	0.33 (0.08)	<.001
Sensitivity	-0.35 (0.12)	0.003	-0.09 (0.12)	0.44	-0.01 (0.12)	0.93	0.26 (0.10)	0.007	0.34 (0.10)	<.001
Attention										
Unadjusted	-0.01 (0.12)	0.92	-0.01 (0.12)	0.96	0.06 (0.13)	0.63	0.01 (0.07)	0.94	0.07 (0.08)	0.34
Adjusted	-0.13 (0.11)	0.24	-0.12 (0.11)	0.28	-0.06 (0.11)	0.59	0.01 (0.08)	0.90	0.07 (0.07)	0.34
Sensitivity	-0.21 (0.14)	0.13	-0.23 (0.14)	0.10	-0.17 (0.14)	0.23	-0.02 (0.09)	0.83	0.04 (0.09)	0.66
Executive Function										
Unadjusted	0.10 (0.07)	0.17	-0.02 (0.07)	0.76	-0.07 (0.07)	0.33	-0.12 (0.06)	0.03	-0.17 (0.06)	0.004
Adjusted	-0.00 (0.07)	0.99	-0.12 (0.07)	0.06	-0.15 (0.07)	0.03	-0.12 (0.06)	0.03	-0.15 (0.06)	0.01
Sensitivity	0.03 (0.08)	0.75	-0.15 (0.09)	0.08	-0.16 (0.09)	0.07	-0.18 (0.07)	0.02	-0.18 (0.07)	0.01
Self-report cognitive difficulties										
Unadjusted	1.2 (1.6)	0.45	-3.1 (1.6)	0.05	-1.3 (1.6)	0.43	-4.3 (1.4)	0.003	-2.5 (1.5)	0.10
Adjusted	0.9 (1.3)	0.50	-1.6 (1.3)	0.24	-1.4 (1.4)	0.30	-2.5 (1.3)	0.06	-2.3 (1.4)	0.09
Sensitivity	-0.3 (1.7)	0.88	-1.8 (1.7)	0.30	-2.4 (1.8)	0.17	-1.6 (1.7)	0.36	-2.2 (1.7)	0.21

<sup>a</sup> $\beta$  estimates (Standard Errors) are from linear mixed models on breast cancer patients. Adjustment includes baseline age, level of education, neurological or psychiatric comorbidities, concomitant anxiety and concomitant cognitive fatigue, and their interactions with time. Sensitivity analyses further adjust for psychotropic drug use, cancer stages, endocrine therapy and Herceptin therapy and their interactions with time.

For all cognitive measures, lower scores indicate poorer cognition.

**Supplementary Table 4.** Multivariable associations of chemotherapy (CT) and other clinical characteristics with cognitive functioning from baseline to 1- and 2-year post-treatment initiation among breast cancer patients.

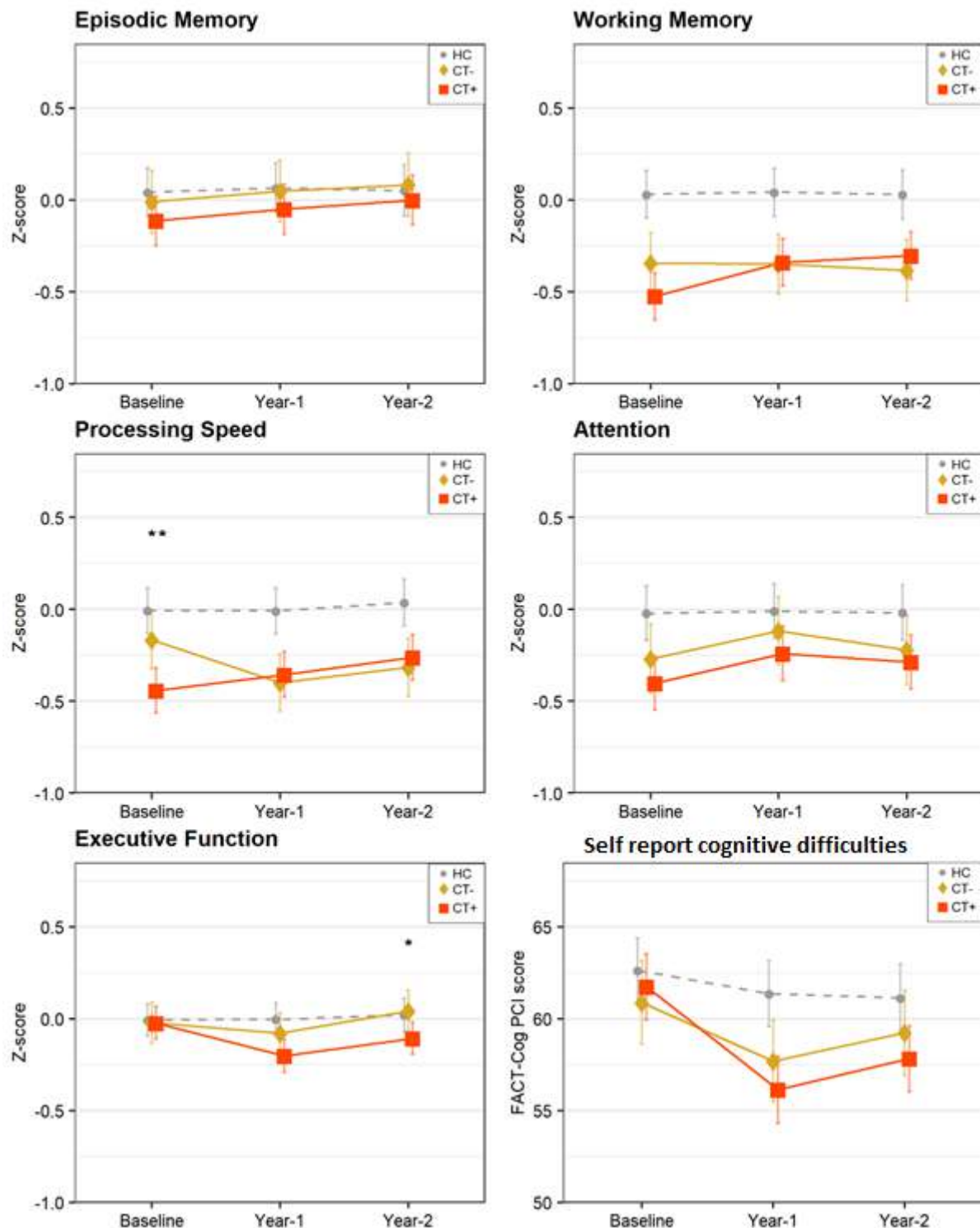
Multivariable associations <sup>a,b</sup>	Pre-tx difference		Pre-tx to Year-1 change difference		Pre-tx to Year-2 change difference	
	$\beta$ (SE)	p	$\beta$ (SE)	p	$\beta$ (SE)	p
	<b>Episodic Memory</b>					
CT+ (vs CT-)	-0.20 (0.13)	0.13	-0.02 (0.13)	0.86	0.10 (0.14)	0.47
Age (for 10y-increase)	-0.15 (0.05)	0.004	0.03 (0.05)	0.52	0.10 (0.05)	0.06
Level of education (for 3y-increase)	0.21 (0.05)	<.001	-0.12 (0.05)	0.03	0.05 (0.06)	0.35
Neurologic/psychiatric history (vs none)	-0.20 (0.13)	0.12	0.05 (0.13)	0.69	-0.09 (0.14)	0.50
Psychotropic medications (vs none)	0.12 (0.21)	0.56	-0.09 (0.21)	0.68	0.10 (0.22)	0.66
Cognitive Fatigue (vs no)	0.01 (0.12)	0.94	-0.20 (0.15)	0.19	0.01 (0.17)	0.98
Anxiety (vs no)	-0.10 (0.09)	0.25	-0.04 (0.13)	0.79	-0.08 (0.14)	0.54
Endocrine therapy (vs no)	-0.10 (0.13)	0.46	0.05 (0.13)	0.73	0.10 (0.14)	0.47
Herceptin therapy (vs no)	0.23 (0.16)	0.15	-0.18 (0.16)	0.25	-0.02 (0.17)	0.92
Cancer stage $\geq$ II (vs <II)	0.06 (0.12)	0.60	0.13 (0.12)	0.29	-0.09 (0.13)	0.46
<b>Working Memory</b>						
CT+ (vs CT-)	-0.33 (0.13)	0.01	0.26 (0.10)	0.007	0.35 (0.10)	<.001
Age (for 10y-increase)	0.01 (0.05)	0.89	-0.06 (0.04)	0.10	-0.06 (0.04)	0.12
Level of education (for 3y-increase)	0.10 (0.05)	0.06	0.09 (0.04)	0.02	0.09 (0.04)	0.03
Neurologic/psychiatric history (vs none)	0.00 (0.13)	0.99	-0.01 (0.09)	0.95	-0.09 (0.10)	0.34
Psychotropic medications (vs none)	-0.20 (0.2)	0.32	0.06 (0.15)	0.69	0.11 (0.16)	0.49
Cognitive Fatigue (vs no)	0.05 (0.09)	0.57	-0.18 (0.11)	0.10	-0.04 (0.12)	0.75
Anxiety (vs no)	0.12 (0.07)	0.07	-0.12 (0.10)	0.22	-0.12 (0.10)	0.24
Endocrine therapy (vs no)	-0.08 (0.13)	0.51	-0.03 (0.10)	0.74	-0.14 (0.10)	0.14
Herceptin therapy (vs no)	0.35 (0.15)	0.02	-0.20 (0.11)	0.08	-0.35 (0.12)	0.003
Cancer stage $\geq$ II (vs <II)	0.15 (0.12)	0.19	-0.08 (0.09)	0.34	-0.10 (0.09)	0.26
<b>Processing Speed</b>						
CT+ (vs CT-)	-0.37 (0.13)	0.004	0.29 (0.10)	0.006	0.37 (0.11)	0.001
Age (for 10y-increase)	-0.14 (0.05)	0.005	0.10 (0.04)	0.009	0.09 (0.04)	0.03
Level of education (for 3y-increase)	0.14 (0.05)	0.008	0.07 (0.04)	0.08	0.12 (0.04)	0.007
Neurologic/psychiatric history (vs none)	0.06 (0.13)	0.62	-0.07 (0.10)	0.46	-0.13 (0.11)	0.23
Psychotropic medications (vs none)	-0.27 (0.20)	0.18	0.11 (0.16)	0.48	0.16 (0.17)	0.34
Cognitive Fatigue (vs no)	-0.06 (0.10)	0.55	-0.09 (0.12)	0.47	-0.11 (0.13)	0.42
Anxiety (vs no)	-0.03 (0.07)	0.73	0.02 (0.10)	0.84	-0.14 (0.11)	0.20
Endocrine therapy (vs no)	0.04 (0.13)	0.77	-0.23 (0.10)	0.03	-0.18 (0.11)	0.09
Herceptin therapy (vs no)	-0.06 (0.15)	0.68	0.19 (0.12)	0.13	0.12 (0.13)	0.35
Cancer stage $\geq$ II (vs <II)	0.16 (0.12)	0.17	-0.01 (0.10)	0.89	-0.10 (0.10)	0.31
<b>Attention</b>						
CT+ (vs CT-)	-0.21 (0.15)	0.16	-0.01 (0.10)	0.93	0.06 (0.10)	0.56
Age (for 10y-increase)	-0.16 (0.06)	0.007	0.02 (0.04)	0.62	0.02 (0.04)	0.62
Level of education (for 3y-increase)	0.28 (0.06)	<.001	-0.03 (0.04)	0.49	-0.04 (0.04)	0.33
Neurologic/psychiatric history (vs none)	0.24 (0.15)	0.11	-0.13 (0.09)	0.17	-0.11 (0.10)	0.28
Psychotropic medications (vs none)	-0.70 (0.24)	0.004	0.21 (0.15)	0.15	0.46 (0.16)	0.004
Cognitive Fatigue (vs no)	-0.04 (0.09)	0.63	-0.06 (0.12)	0.60	0.23 (0.13)	0.07
Anxiety (vs no)	-0.04 (0.07)	0.62	-0.07 (0.10)	0.47	0.03 (0.10)	0.76
Endocrine therapy (vs no)	-0.24 (0.15)	0.12	-0.11 (0.10)	0.27	-0.14 (0.10)	0.16
Herceptin therapy (vs no)	0.02 (0.18)	0.89	-0.11 (0.12)	0.32	-0.08 (0.12)	0.49

Cancer stage $\geq$ II (vs <II)	0.08 (0.14)	0.56	0.07 (0.09)	0.43	0.03 (0.09)	0.73
Executive function						
CT+ (vs CT-)	0.01 (0.09)	0.89	-0.17 (0.08)	0.03	-0.18 (0.08)	0.02
Age (for 10y-increase)	-0.14 (0.03)	<.001	-0.01 (0.03)	0.70	0.04 (0.03)	0.18
Level of education (for 3y-increase)	0.17 (0.04)	<.001	-0.02 (0.03)	0.42	-0.05 (0.03)	0.10
Neurologic/psychiatric history (vs none)	-0.10 (0.09)	0.27	-0.03 (0.07)	0.67	0.06 (0.08)	0.44
Psychotropic medications (vs none)	-0.13 (0.14)	0.35	0.06 (0.12)	0.60	0.05 (0.13)	0.66
Cognitive Fatigue (vs no)	0.06 (0.07)	0.42	-0.18 (0.09)	0.040	-0.12 (0.10)	0.20
Anxiety (vs no)	-0.11 (0.05)	0.031	0.03 (0.07)	0.67	0.02 (0.08)	0.82
Endocrine therapy (vs no)	-0.03 (0.09)	0.73	0.02 (0.08)	0.82	0.10 (0.08)	0.20
Herceptin therapy (vs no)	0.00 (0.10)	0.99	0.00 (0.09)	0.99	0.04 (0.09)	0.70
Cancer stage $\geq$ II (vs <II)	-0.07 (0.08)	0.37	0.10 (0.07)	0.14	0.10 (0.07)	0.17
Self-report cognitive difficulties						
CT+ (vs CT-)	-0.1 (1.9)	0.94	-1.3 (1.9)	0.49	-2.2 (1.9)	0.27
Age (for 10y-increase)	-0.1 (0.7)	0.85	1.1 (0.7)	0.13	0.0 (0.7)	0.97
Level of education (for 3y-increase)	0.2 (0.8)	0.79	0.7 (0.8)	0.34	0.9 (0.8)	0.27
Neurologic/psychiatric history (vs none)	-0.1 (1.8)	0.97	-0.7 (1.8)	0.71	0.4 (1.9)	0.84
Psychotropic medications (vs none)	-9.7 (2.9)	0.001	9.4 (2.9)	0.001	3.2 (3.1)	0.31
Cognitive Fatigue (vs no)	-7.1 (1.7)	<.001	-3.8 (2.1)	0.08	-0.8 (2.4)	0.73
Anxiety (vs no)	-5.2 (1.3)	<.001	-1.1 (1.8)	0.54	-1.3 (1.9)	0.48
Endocrine therapy (vs no)	-0.7 (1.8)	0.71	-1.2 (1.9)	0.53	-0.5 (1.9)	0.80
Herceptin therapy (vs no)	0.1 (2.2)	0.96	1.0 (2.2)	0.64	0.3 (2.3)	0.89
Cancer stage $\geq$ II (vs <II)	2.1 (1.7)	0.23	-2.3 (1.7)	0.20	-0.7 (1.8)	0.71

<sup>a</sup>  $\beta$  estimates (Standard Errors) are from linear mixed models.

<sup>b</sup> For all cognitive measures, lower scores indicate poorer cognition.

**Supplementary Figure 1.** Predicted cognitive measures of breast cancer patients treated with chemotherapy (CT+), without chemotherapy (CT-) and healthy controls (HC) from baseline to 1- and 2-year post-treatment initiation



\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  for CT+ vs CT- comparison of scores estimates at a given time point. Estimates are from linear mixed models adjusted for baseline age, level of education, neurological or psychiatric comorbidities, concomitant anxiety, concomitant cognitive fatigue, and their interactions with time. Curves are plotted for an average study participant profile (an individual aged 54y, with 13y of schooling, no previous history of neurologic/psychiatric condition, no cognitive fatigue nor anxiety). For all cognitive measures, lower scores indicate poorer cognition.