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ORIGINAL ARTICLE

Electroencephalogram power changes as a correlate of chemotherapy-associated fatigue and cognitive dysfunction

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Abstract
Purpose Persistent fatigue and cognitive dysfunction are poorly understood potential long-term effects of adjuvant chemotherapy. In this pilot study, we assessed the value of electroencephalogram (EEG) power measurements as a means to evaluate physical and mental fatigue associated with chemotherapy.
Patients and methods Women planning to undergo adjuvant chemotherapy for breast cancer and healthy controls underwent neurophysiologic assessments at baseline, during the time of chemotherapy treatment, and at 1 year. Repeated measures analysis of variance was used to analyze the data.
Results Compared with controls, patients reported more subjective fatigue at baseline that increased during chemotherapy and did not entirely resolve by 1 year. Performance on endurance testing was similar in patients versus controls at all time points; however, values of EEG power increased after a physical task in patients during chemotherapy but not controls. Compared with controls, subjective mental fatigue was similar for patients at baseline and 1 year but worsened during chemotherapy. Patients performed similarly to controls on formal cognitive testing at all time points, but EEG activity after the cognitive task was increased in patients only during chemotherapy.
Conclusion EEG power measurement has the potential to provide a sensitive neurophysiologic correlate of cancer treatment-related fatigue and cognitive dysfunction.

Keywords Chemobrain · Breast cancer · Cognitive effects · Fatigue

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Introduction

Adjuvant chemotherapy for early stage breast cancer improves prospects for long-term survival. Although most chemotherapy related toxicities are expected to resolve soon after completion of treatment, a subset of survivors report long-term problems with fatigue and cognitive dysfunction [1–3]. These issues can lead to significant impairment in quality of life. Sorting out to what extent such symptoms are directly related to chemotherapy versus hormonal changes, normal aging, and coexisting medical or psychological conditions is challanging. Management is also complicated by the often subjective nature of physical and mental fatigue, leading to difficulties in evaluating the severity of symptoms or the impact of interventions. Better understanding of physiologic correlates of chemotherapy-related fatigue and cognitive dysfunction may provide objective means to evaluate patients as well as assess the efficacy of therapeutic interventions.

Alteration of central nervous system signals has been demonstrated with electroencephalography in patients with advanced cancer-related fatigue undertaking a standard motor task [4]. In that population, muscle fatigue during the motor task correlated with subjective fatigue and with altered central nervous system (CNS) signals, suggesting a centrally mediated inability to recruit muscle as an underlying mechanism of cancer-related fatigue [4]. Such alterations in CNS signaling have also been observed in patients with chronic fatigue syndrome [5]. Whether similar changes in CNS signaling occur in chemotherapy-associated fatigue and cognitive dysfunction has not been previously reported.

In this pilot study, neurophysiologic testing was performed on women undergoing curative intent chemotherapy for breast cancer prior to, during, and after recovery from chemotherapy. A healthy control group was evaluated with the same battery of tests at similar time intervals. At each time point, participants were evaluated for both subjective and objective

measures of fatigue and cognitive impairment. Electroencephalography (EEG) recordings were obtained at rest and following performance of cognitive and physical tasks.

Methods

Subjects

Women with stage I–III breast cancer, who had completed surgery, were clinically free of active cancer and who were planning to undergo adjuvant chemotherapy were enrolled. Control subjects who were female friends or family members of similar age (+/−10 years) to the patient subjects were also enrolled. Participants had no history of significant cardiovascular disease, stroke, polyneuropathy, amyotrophy, myosthenic syndrome, or pulmonary compromise. All subjects gave informed consent. The experimental procedures were approved by the institutional review board of the Case Comprehensive Cancer Center.

Study assessments were performed on patients prior to the first chemotherapy treatment ("baseline assessment"), after three or four cycles of adjuvant chemotherapy, but not within 1 week of the most recent treatment ("treatment assessment") and at approximately 1 year from initial enrollment ("recovery assessment"). Control subjects were assessed at the same time intervals concurrently with their respective friend or family member patient subject. At each assessment, subjects underwent evaluations for fatigue, depression, performance on a motor task, subjective cognitive function, objective cognitive testing, and EEG measurements at rest as well as following the motor and cognitive tasks. In addition, subjects rated perceived effort during the motor task.

Assessment scales

Assessment scales were chosen that were brief and relatively simple to administer. A ten-question Brief Fatigue Inventory (BFI) [6] was used as a subjective measure of fatigue. Screening for depression was done with a BDI-Fast Screen assessment [7]. A nine-question Brief Mental Fatigue Questionnaire (BMF) [8] was used as a subjective measure of cognitive function. The Borg 15-category scale was used to determine perceived exertion during the physical task.

Motor task to induce fatigue

Subjects were instructed to perform a sustained elbow flexion at 30 % of their maximum elbow flexion force until reaching perceived exhaustion. Patients were tested using the nonsurgical arm, and controls used the dominant or nondominant arm according to what was used by their paired patient subject. Fatigability was quantified as endurance time (ET) defined as duration from the beginning of the sustained muscle contraction to the point where force drops by 10 % from the target level by more than 2 s.

Cognitive task

Symbol Search and Digit Symbol-Coding tests, two nonverbal processing speed subtests of the Wechsler Adult Intelligence Scale-III were administered to participants. The Symbol Search test is a 2-min timed test that requires the subject to visually scan two groups of symbols, a target group (two symbols) and a search group (five symbols). The subject must assess whether either of the target symbols matches any of the search group symbols. The Digit Symbol-Coding test, also a 2-min timed test, assesses visual-motor coordination, motor and mental speed, as well as scanning accuracy. In this test, a symbol key is provided in which digits 1 through 9 are each paired with a unique symbol. Subjects must copy the appropriate symbols in a box below randomly presented target numbers as quickly and accurately as possible. Together, the Symbol Search and Digit Symbol-Coding test results can be used to calculate a Processing Speed Index.

Electroencephalography

EEG signals were recorded continuously from the scalp at rest and after the cognitive and motor tasks using a 128-channel EEG data acquisition system. High-density scalp EEG was recorded with 128 Ag-AgCl electrodes embedded in a Geodesic Sensor Net. The distance between neighboring electrodes in the net is approximately 3 cm. EEG signals were amplified (×75,000), filtered (0.1–100 Hz), and digitized 500 samples/s. The regional sources activities that were used for analysis were located in the left and right central brain regions. The signal magnitude reflects the estimated source activity if only one brain region is active.

EEG frequency analysis was performed to determine fatigue-related central nervous system signal changes in the frequency domain. Fast Fourier Transform (FTT) was applied on consecutive 6-s-long segments of data free of eye blinks and other artifacts. Absolute values of EEG power were expressed in nAm^2.

Data analysis

Repeated measures of analysis of variance were used to compare subjects and controls at specific time points and to compare findings during treatment and after recovery relative to baseline within each group. All statistical tests were two-sided. The analyses are not adjusted for multiple comparisons so $p<0.05$ was used to indicate statistical significance. The spacial deconvolution FOCUS method was used to analyze the EEG data.

Results

Patients

Of nine patient/control pairs enrolled in this study, one pair withdrew consent prior to any study evaluations due to scheduling difficulties. Findings from the 16 subjects (8 patients and 8 controls) undergoing protocol evaluations are included here. One pair was unable to complete the final assessment due to a second cancer diagnosis requiring additional therapy.

Age was similar for patients (53 +/−6 years) and controls (54 +/−6 years). Chemotherapy regimens for the patients consisted of doxorubicin and cyclophosphamide followed by paclitaxel (five patients), docetaxel and cyclophosphamide (two patients), and docetaxel, Carboplatin plus trastuzumab (one patient). All seven patients completing the final assessment were receiving adjuvant endocrine therapy by that time (2 tamoxifen, and 5 aromatase inhibitors). No difference is observed in depression screening between patients and controls or at the different time points. Additional results are described in Table 1.

Measurements of physical and mental fatigue

A trend is observed for greater subjective fatigue, measured by BFI scores, in patients than controls at baseline ($p=0.08$). Reported fatigue is significantly greater for patients during chemotherapy ($p<0.001$) and remains greater at 1 year compared with controls. Subjective fatigue is also significantly greater among patients during chemotherapy than at their baseline ($p=0.037$). Physical endurance (Fig. 1) and perception of effort during the motor task, however, did not change significantly in either group at the different time points.

Subjective mental fatigue, measured by the BMF, is similar for patients and controls at baseline. Reported mental fatigue worsens for patients during chemotherapy compared with the control group ($p=0.033$) but there is no difference in BMF scores at 1 year. Objective cognitive function, measured by Processing Speed Index, was stable at all three time points for both groups (Fig. 2).

EEG measurements

EEG power values presented in Table 1 reflect the total spectrum of EEG power recorded from the left central brain region, covering an area of approximately 16 electrodes. EEG power at baseline and at 1 year are similar among patients and controls and values do not change significantly from rest following either the physical or cognitive task. During the time of chemotherapy treatment, however, EEG power value is increased for patients relative to controls at rest ($p=0.05$) and following both the physical ($p<0.001$) and cognitive ($p<0.001$) tasks. Furthermore, patients receiving

Table 1 Mean (and standard deviations) for measurements of physical and mental fatigue as well as EEG power measurements

	Baseline (SD)	Treatment (SD)	Recovery (SD)
Brief mental fatigue score			
Patient	8 (6)	14 (10)	12 (12)
Control	6 (5)	5 (4)	8 (12)
p value	0.74	0.033	0.34
Processing speed index			
Patient	107 (11)	109 (10)	111 (8)
Control	109 (16)	112 (16)	113 (15)
p value	0.82	0.57	0.76
Brief fatigue inventory			
Patient	20 (18)	36 (23)	28 (22)
Control	6 (5)	7 (5)	7 (7)
p value	0.08	<0.001	0.016
Endurance time (seconds)			
Patient	387 (223)	354 (142)	440 (108)
Control	324 (120)	348 (136)	357 (94)
p value	0.39	0.93	0.29
EEG power at rest			
Patient	221 (164)	451 (400)	140 (150)
Control	183 (114)	131 (77)	98 (52)
p value	0.81	0.05	0.81
EEG power after cognitive task			
Patient	262 (214)	1,010 (826)	217 (273)
Control	199 (94)	173 (139)	143 (94)
p value	0.69	<0.001	0.67
EEG power after physical task			
Patient	264 (179)	875 (737)	277 (188)
Control	180 (101)	180 (106)	319 (347)
p value	0.61	<0.001	0.81

p values are patient versus control

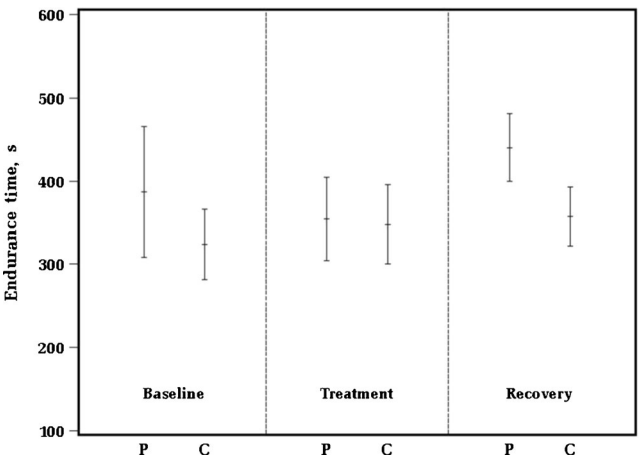

Fig. 1 Physical endurance time is similar for patients and controls at all three time points. *P* patients, *C* controls

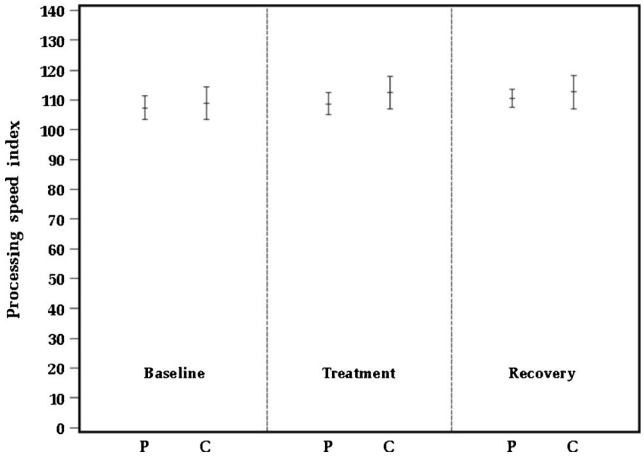

Fig. 2 Processing Speed Index is similar for patients and controls at all three time points. *P* patients, *C* controls

chemotherapy demonstrate an increase in EEG power values from rest following both the physical (p=0.06) and cognitive tasks (p=0.012). No significant change from rest following the physical and mental tasks is observed for controls at any time point or for patients at the baseline and 1 year assessments. (Figs. 3 and 4).

The relationship between brain activity and fatigue is explored in a post-hoc analysis by creating an additional variable: total spectrum EEG change (TSEC), which represents the difference between EEG power following the cognitive task and baseline. TSEC correlates significantly with self-rated fatigue (r=0.59, p=0.02; Fig. 5a) when the entire sample is considered in the analysis. There is a trend toward a positive correlation in the patient subgroup, although neither subgroup showed a statistically significant correlation due, at least in part, to small sample size (patients r=0.32, p=0,32; controls r=.07, p=0.85; Fig. 5b).

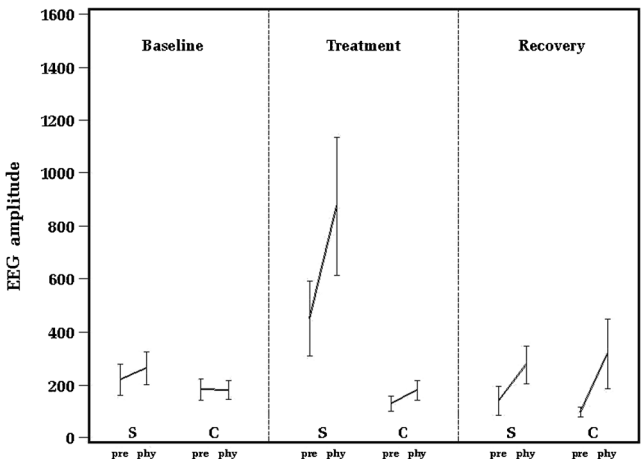

Fig. 3 Patients and controls are similar at baseline and recovery before and after the physical task. EEG power at rest is increased for patients relative to controls and further increases after a physical task during treatment only. *P* patients, *C* controls, *Pre* at rest, *cog* after the cognitive task

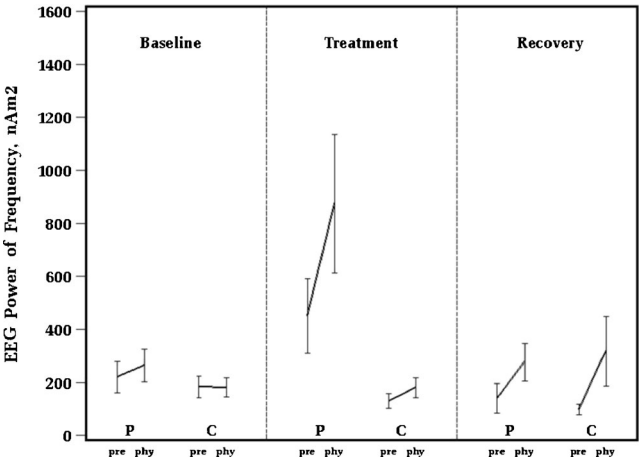

Fig. 4 Patients and controls are similar at baseline and recovery before and after the cognitive task. EEG power at rest is increased for patients relative to controls and further increases after a cognitive task during treatment only. P=patients, C=controls, *Pre* at rest, *phy* after the physical task

Discussion

In this pilot study, EEG measurements following physical and cognitive tasks along with both subjective and objective

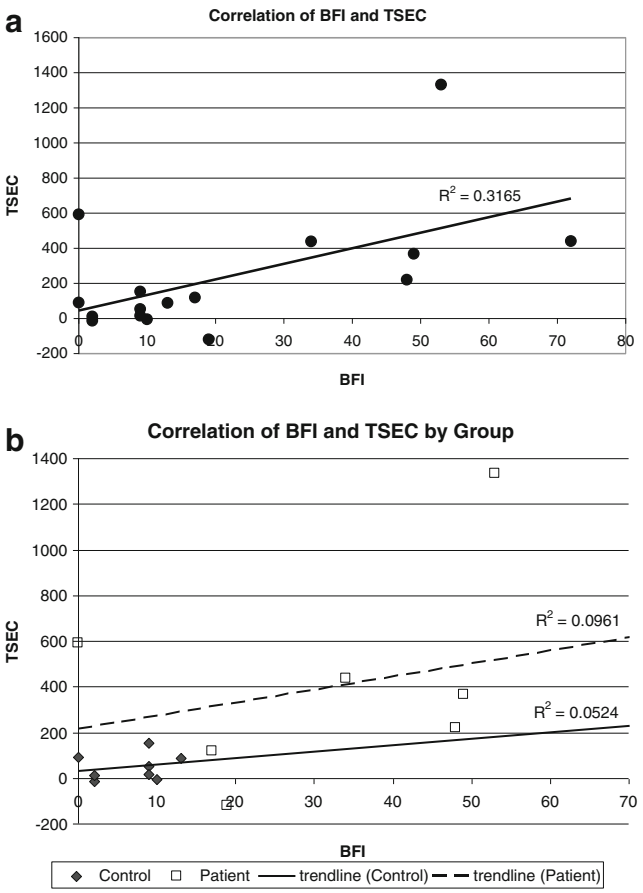

Fig. 5 **a** Total spectrum EEG change (*TSEC*) during treatment correlates with self-reported fatigue. **b** The relationship between TSEC and self reported fatigue by BFI is stronger for patients than for controls

assessments of physical and mental fatigue were successfully obtained in patients undergoing treatment for early stage breast cancer and a control group at various time points with respect to chemotherapy treatments. Breast cancer patients reported greater physical fatigue at all time points but particularly during the time of chemotherapy treatment. Patients reported worsening mental fatigue only during chemotherapy.

Previous studies evaluating persistence of cognitive dysfunction following chemotherapy have demonstrated variable results. A recent study by Koppelmans et al. suggested that cognitive impairment from cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy may persist for more than 20 years [9]. In an earlier study, CMF chemotherapy was associated with an increased risk of cognitive impairment at 2 years compared with a control population but fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy was not associated with an increase in cognitive dysfunction at 2 years [10]. In addition, improvement in cognitive function was observed from year 2 to year 4 for subjects who had received both CMF and FEC regimens.

In the present study, EEG changes observed among patients, as well as the perception of cognitive dysfunction, had resolved by 1 year. The small size of this study limits our ability to detect modest differences between patients and controls; however, the findings are consistent with other studies suggesting that most patients receiving nonmethotrexate containing chemotherapy will largely recover from chemotherapy associated cognitive effects over time.

In the small group of participants evaluated in this study, an objective measure of processing speed and objective physical endurance testing were insensitive means to measure differences in patients versus controls and in patients during chemotherapy versus other time points. EEG testing, however, demonstrated significant alterations in brain activity among patients versus controls during chemotherapy treatment. Such alterations in brain activity were heightened following mental and physical tasks during treatment but not at other time points, and no such change was observed in controls.

The observed increase in EEG power during chemotherapy which further increases following physical and mental tasks, suggests more intense activation of neural structures associated with chemotherapy-related mental and physical fatigue. While patient subjects were able to maintain good performance on cognitive and physical tasks during chemotherapy, the EEG changes may reflect a greater effort required to achieve the results. This hypothesis is supported by our exploratory findings which suggest that greater increases in EEG power during task performance are associated with higher self-rated fatigue. Indeed, in other conditions affecting cognitive function, such as concussion, multiple sclerosis, and mild cognitive impairment, functional brain imaging studies have revealed hyperactivation of various brain regions compared with control subjects. It has been speculated that this increase in activity plays a compensatory role, serving to maintain normal cognitive function despite neuropathology [11]. To our knowledge, the current study is the first to demonstrate EEG findings suggesting that an increase in brain activity may explain stable performance on cognitive and physical tasks in spite of increased fatigue.

For a subset of patients experiencing persistent fatigue and cognitive impairment following chemotherapy, better understanding of the neurophysiology of this problem and effective interventions are needed. The availability of a sensitive and objective tool for measuring cognitive effects of chemotherapy should facilitate the evaluation of interventions designed to treat or prevent this troublesome late effect of chemotherapy. Scalp EEG has potential as a novel and noninvasive means for measuring a correlate of mental and physical fatigue associated with chemotherapy.

Conflict of interest None

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