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**Clinical Correspondence**

# Quantitative electroencephalography biomarkers of cognitive complaints after adjuvant therapy in breast cancer survivors: a pilot study

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Dear Editor,

Cognitive complaints are pervasive among breast cancer survivors (BCS), yet their biology is not well understood. Complaints are only partly reflected in neuropsychological test performance [1]. Moreover, their etiology is likely multifactorial; such complaints have been linked not only to adjuvant therapies ('chemobrain' phenomenon) but also to the development of cancer itself [2]. In fact, biologic processes including DNA damage, oxidative stress, inflammation, and shortened telomeres have been shown to underlie both cancer progression and the impact of cancer treatments; further, these same processes are related to aging and cognitive decline [3]. Models of aging therefore have been proposed as a framework for studying cognitive dysfunction in BCS [4].

Resting-state quantitative electroencephalography (qEEG) offers an indicator of brain function that has been related to aging and cognitive function [5]. Changes in the resting-state EEG have been linked to cognitive decline in normal aging and to cognitive deficits in mild cognitive impairment (MCI) and Alzheimer's disease. An overarching pattern is one of the shifts in EEG power from higher (beta and alpha) to lower (theta and delta) frequencies with decreased cognitive status. Physiologic tests such as qEEG constitute a reproducible objective measure that could complement performance measures. In this vein, we explored resting-state qEEG measures as correlates of cognitive complaints in a cross-section of well-characterized BCS.

## Methods

### Participants and recruitment

Participants were recruited from the University of California, Los Angeles (UCLA) cognitive rehabilitation study (CRS)

for BCS with cognitive complaints [6] and the UCLA mind body study (MBS)—a prospective study of early stage, posttreatment breast cancer patients [1]. All patients had been treated for stage 0, I, II, or IIIA breast cancer and were on no active cancer therapy other than possible endocrine therapy. For CRS, patients had to have increased cognitive complaints to enter the rehabilitation intervention trial, and for MBS, there were no selection criteria other than the exclusion of health conditions that would interfere with the assessment of study outcomes. Across protocols, exclusions were evidence of current or past central nervous system or medical disorder/disease that might be expected to impact cognitive functioning (e.g., multiple sclerosis, thyroid dysfunction); history of head trauma with loss of consciousness greater than 30 min; epilepsy, dementia, or severe learning disability; current mood, anxiety, or psychotic disorder, or current substance abuse or dependence; and history of whole-brain irradiation or brain surgery. These same criteria were applied during recruitment to the secondary, qEEG study. Participants were treated in accordance with the Declaration of Helsinki. Experimental procedures were approved by the UCLA Institutional Review Board, and all participants provided written informed consent.

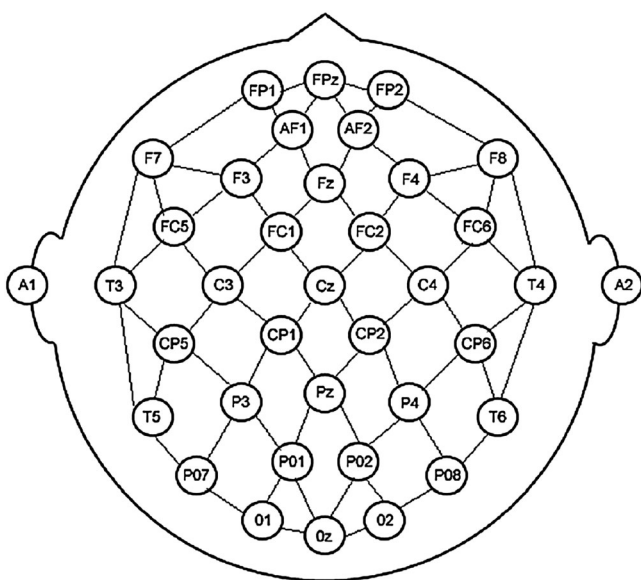
### Clinical assessments

Participants completed the Patient's Assessment of Own Functioning Inventory (PAOFI) at the time of the EEG assessment. This 33-item self-report questionnaire has been used previously in studies of cognitive complaints in BCS [7]. The PAOFI assesses the frequency with which an individual experiences difficulties in four functional domains: memory (MEM), higher-level cognition (HLC), language and communication (LC), and motor sensory

processing. Individual items are rated on a 6-point Likert scale. Items rated as 'almost always', 'very often', and 'fairly often' were assigned 1 point, whereas items rated 'once in awhile', 'very infrequently', or 'almost never' were given 0 points [cf. 8].

### Quantitative electroencephalography techniques

Electroencephalograph (EEG) recordings were obtained while subjects rested in the eyes-closed, maximally alert state [cf. 9]. Thirty-five Ag/AgCl recording electrodes were positioned with an electrode cap (ElectroCap, Inc.; Eaton, OH) using an extended International 10–20 system with linked ears reference (Figure 1). Subjects were alerted to avoid drowsiness and were instructed to remain still and inhibit blinks or eye movements during each recording. Electrode impedances were balanced and were maintained below 5 k $\Omega$  for all channels. Vertical and horizontal electrooculograms were recorded to identify eye movement artifact using bipolar electrodes placed at the supraorbital and infraorbital ridges of the right eye and at the outer canthi of both eyes. A minimum of 10 min of EEG data were recorded using a 16-bit resolution NeuroScan system (Compumedics, Inc.; Charlotte, NC) at a sampling rate of 256 Hz, with a high-frequency filter of 70 Hz, a low-frequency filter of 0.3 Hz, and a notch filter at 60 Hz. Data were imported into Brain Vision Analyzer software (Brain Products GmbH; Gilching, Germany) to remove offsets, optimize scaling, and segment the data into 2-s nonoverlapping epochs. Two technologists inspected the data independently using multiple bipolar and referential montages to isolate, and then remove, any segments containing eye movement, muscle-related or movement-related artifacts, or amplifier drift.



**Figure 1.** Thirty-five recording electrodes were positioned using a standard extension of the International 10–20 system

The Brain Vision Analyzer fast Fourier transform function was used to calculate the power spectral frequency. The 512-point fast Fourier transform was calculated for artifact-free 2-s epochs without windowing, with 0.5 Hz overlap at the limits of the band, yielding a frequency resolution of 0.5 Hz. Absolute power ( $\mu\text{V}^2$ ) and relative power (percentage of total power) were calculated for each channel in delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–20 Hz).

### Data analysis

Pearson's  $r$  was used to examine bivariate correlations between cognitive complaints and EEG measures. Cognitive measures included the PAOFI total and the three subscales on which women in the parent study showed deficits as compared with healthy controls either at baseline (MEM, HLC) [8] or at 1-year follow-up (LC; unpublished data). EEG measures included 'global' (average of all 35 channels) absolute and relative power measures in the four frequency bands, followed by analyses at each electrode to detect any regional patterns that might be obscured by the whole-head averaging. Analyses were conducted using SPSS version 20 with set at  $p \leq 0.05$  without correction for multiple comparisons.

## Results

### Clinical and demographic characteristics

Twenty-seven women were recruited (8 from CRS and 19 from MBS), the majority of whom had received adjuvant therapy (Table 1). Twelve women (44%) scored  $>1$  standard deviation above the mean of the healthy reference sample [8] on the PAOFI total.

**Table 1.** Clinical and demographic characteristics of the sample

	Total sample (n = 27)
Age (mean years $\pm$ SD)	52.4 $\pm$ 5.0
Chemotherapy	21 (78%)
Time since chemotherapy (months)	27.9 $\pm$ 3.9
Radiation therapy	22 (81%)
Chemo + radiation	18 (67%)
Endocrine therapy	22 (81%)
IQ (WTAR) <sup>a</sup> (mean $\pm$ SD)	113.3 $\pm$ 8.3
BDI-II total (mean $\pm$ SD) <sup>b</sup>	8.5 $\pm$ 5.8; range: 0–25
PAOFI (mean $\pm$ SD)	
Total (33 items)	4.63 $\pm$ 4.41
MEM	2.26 $\pm$ 2.46
HLC	0.70 $\pm$ 1.35
LC	1.37 $\pm$ 1.42

SD, standard deviation; WTAR, Wechsler Test of Adult Reading; BDI-II, Beck Depression Inventory II; PAOFI, Patient's Assessment of Own Functioning Inventory; MEM, memory; HLC, higher-level cognition; LC, language and communication.

<sup>a</sup>Full-scale IQ was estimated in the parent studies [1] using WTAR.

<sup>b</sup>BDI-II is calculated without the item pertaining to concentration.

### Quantitative electroencephalography results

Global absolute or relative power measures were not significantly associated with PAOFI total, or with MEM or HLC subscales. However, higher global absolute delta and theta power were associated with greater complaints on the LC subscale ( $r=0.417$ ,  $p=0.030$ , and  $r=0.403$ ,  $p=0.037$ , respectively). Partial correlations controlling for age remained significant for delta  $r=0.402$ ,  $p=0.042$ , and showed a trend relationship for theta ( $r=0.381$ ,  $p=0.055$ ).

Lower relative beta power was significantly associated with higher PAOFI total complaints at 13 of 35 scalp electrodes, primarily from temporal, parietal, and occipital regions ( $r$  range:  $-0.401$  to  $-0.482$ ;  $p$  range:  $0.011$ – $0.038$ ) and with greater LC complaints at eight posterior electrodes (O1, O2, Oz, Po1, Po2, Po7, Po8, and T6) with  $r$  range:  $-0.381$  to  $-0.407$ ,  $p$  range:  $0.035$ – $0.050$  (refer to Figure 1 for electrode placements). No associations were observed with MEM or HLC subscales.

### Discussion

Breast cancer survivors with higher cognitive complaints, specifically in LC, showed a global ‘slowing’ of the EEG, as evidenced by increased global absolute power in the slower delta and theta brain wave frequencies. Whereas this pattern is typically characteristic of advancing age [5], increases in the slowest frequency (delta) were associated with complaints even when controlling for subjects’ chronological age. This observation is consistent with a hypothesis that models of aging may prove useful in conceptualizing cognitive complaints in this population [4]. Additionally, overall cognitive complaints were associated with temporoparietal and occipital decreases in relative beta power. Dysfunction within these brain regions would be consistent with LC functioning complaints. Moreover, a selective loss of relative beta activity has been reported with MCI and early dementia in elders [10], providing further possible links among cognitive

complaints in BCS, brain function assessed in the resting-state EEG, and cognitive dysfunction in advanced age.

Results of this pilot study support the potential utility of resting-state EEG measures in helping to elucidate neurophysiology underlying cognitive complaints in BCS. Future studies should use qEEG to examine relationships between brain function and cognitive complaints in larger cohorts that would allow for statistical analyses of covariates and multivariable models.

### Acknowledgements

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### Conflict of interest

The authors declare that they have no conflict of interest.

### Key points

- Cognitive complaints in BCS are pervasive, but the underlying physiology is poorly understood. Models of aging maybe helpful in guiding research in on cognitive complaints in BCS.
- Models of aging maybe helpful in guiding research in on cognitive complaints in BCS.
- Resting-state qEEG measures of brain function have previously been associated with aging and cognitive deficits.
- We assessed resting-state EEG parameters in a cross-section of 27 BCS and found greater self-report complaints associated with an overall slowing of the EEG, with some features similar to patterns seen in aging, MCI, and Alzheimer’s disease.
- qEEG biomarkers should be studied more extensively in larger cohorts as they may provide an objective measure of neurophysiological dysfunction linked to cognitive complaints in BCS.

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