Clinical Neurophysiology 127 (2016) 369–378

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Sustained attention abnormalities in breast cancer survivors with cognitive deficits post chemotherapy: An electrophysiological study

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ARTICLE INFO

Article history:
Accepted 10 March 2015
Available online 21 March 2015

Keywords:
Sustained attention
Mind wandering
Adjuvant chemotherapy
Breast cancer
Cognitive deficits
P300 ERP
Rest EEG

HIGHLIGHTS

- Our study examined if the ability to maintain sustained attention could be a feature of the cognitive difficulties reported by some breast cancer survivors (BCS).
- We found that BCS were less likely to maintain attention towards the task, and displayed reduced P3 amplitude to task relevant stimuli relative to healthy controls.
- This data underscores the utility of a new combination of laboratory-based measures for assessing self-reported attentional impairments in BCS.

ABSTRACT

Objective: Many breast cancer survivors (BCS) report cognitive problems following chemotherapy, yet controversy remains concerning which cognitive domains are affected. This study investigated a domain crucial to daily function: the ability to maintain attention over time.
Methods: We examined whether BCS who self-reported cognitive problems up to 3 years following cancer treatment ($n = 19$) performed differently from healthy controls (HC, $n = 12$) in a task that required sustained attention. Participants performed a target detection task while periodically being asked to report their attentional state. Electroencephalogram was recorded during this task and at rest.
Results: BCS were less likely to maintain sustained attention during the task compared to HC. Further, the P3 event-related potential component elicited by visual targets during the task was smaller in BCS relative to HC. BCS also displayed greater neural activity at rest.
Conclusions: BCS demonstrated an abnormal pattern of sustained attention and resource allocation compared to HC, suggesting that attentional deficits can be objectively observed in breast cancer survivors who self-report concentration problems.
Significance: These data underscore the value of EEG combined with a less traditional measure of sustained attention, or attentional states, as objective laboratory tools that are sensitive to subjective complaints of chemotherapy-related attentional impairments.

1. Introduction

Cognitive impairments are commonly reported by breast cancer survivors (BCS) who have undergone post-operative adjuvant chemotherapy, with a reported prevalence of 17–75% (Ahles et al., 2002; Brezden et al., 2000; Ganz et al., 2013; Kreukels

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http://dx.doi.org/10.1016/j.clinph.2015.03.007
1388-2457/

et al., 2006; Schagen et al., 1999, 2001; van Dam et al., 1998). These cognitive complaints are associated with reduced quality of life and emotional well-being (van Dam et al., 1998; Schagen et al., 1999; Ahles et al., 2002), which highlights the importance of establishing objective measures of these deficits and their underlying neural mechanisms. While recent meta-analyses found a small to medium effect of chemotherapy in the post-treatment period on verbal and visuospatial abilities (Jim et al., 2012) as well as memory and attentional abilities (Lindner et al., 2014), research has yet to converge on a reliable profile of these cognitive impairments (e.g., Jansen et al., 2011; Kreukels et al., 2005, 2006, 2008a,b; Lepage et al., 2014; Quesnel et al., 2009; Tager et al., 2010; Wefel et al., 2015). Thus far, the focus has been on identifying a profile of deficits as indexed by a wide range of neuropsychological tests covering multiple sensory-motor and cognitive domains (Jansen et al., 2011; Quesnel et al., 2009; Tager et al., 2010; Wefel et al., 2011), yet to date this has lacked specificity in determining the effects of chemotherapy on a particular cognitive function. Despite concentration problems being one of the most common cognitive complaints by BCS (van Dam et al., 1998; Schagen et al., 1999), few studies have specifically addressed post-chemotherapy changes in the ability to maintain attention on the current task.

Sustained attention is an important cognitive domain that is crucial to our daily functioning, and can have a substantial impact on numerous other areas of cognitive function. It serves the purpose of focusing attention over time on a salient, task-relevant input to which neural resources are allocated, while simultaneously disregarding distractors not relevant to the task-at-hand. Recent research has revealed mixed findings regarding attentional abilities in BCS. For instance, Chen et al. (2014) reported that the alerting and executive control aspects of attentional networks were selectively impaired in BCS who have received adjuvant chemotherapy compared to BCS who did not. Likewise, BCS also performed poorly on tasks that require concentration, such as the Digit Span and Digit Symbol tests (Schagen et al., 1999). In contrast, other studies showed intact attentional abilities in BCS (Ahles et al., 2002; van Dam et al., 1998). The inconsistency of these findings may stem from the variety of tasks used to assess attention and the fact that performance on some attention tasks likely involves other cognitive processes that may also be impaired in BCS, including response inhibition and psycho-motor functioning.

In our daily life, successful performance on a task typically requires sustained attention for a time much longer than that used in experimental trials, which require focused attention for relatively short intervals of time and in which performance is evaluated on a trial-by-trial basis. Given a relatively inconsistent correspondence between subjective cognitive complaints and objective cognitive task performance assessed in the laboratory (Ahles et al., 2002; Pullens et al., 2010; Schagen et al., 1999; van Dam et al., 1998), one potential explanation is that BCS can perform competently when they focus their attention on a relatively short laboratory task. Unlike each experimental task within a neuropsychological test battery that typically lasts a few minutes, the completion of a house chore or work assignment generally takes much more time. In losing their concentration as commonly reported (van Dam et al., 1998; Schagen et al., 1999; Kreukels et al., 2006), BCS may also consequently lose their ability to perform their task-at-hand. Accordingly, we aimed to address the potential effects of chemotherapy on the ability to stay on-task for an extended period of time.

Our attention towards an ongoing task naturally waxes and wanes over time. On average, the general population report being off-task or mind wandering around 30–50% of the time, suggesting it is a regularly occurring experience that occupies a notable portion of our mental life (Killingsworth and Gilbert, 2010). In the context of an experiment, mind wandering is characterized as our attention drifting away from the demands of the external environment, or the processing required by the task-at-hand, towards the internal milieu. Converging lines of evidence suggest that mind wandering is associated with an attenuation of a broad array of neurocognitive processing (O'Connell et al., 2009; Barron et al., 2011; Kam and Handy, 2013; Kam et al., 2014). Moreover, there is a robust relationship between mind wandering episodes and performance failure, as observed in both experimental tasks conducted in the laboratory (Smallwood et al., 2003; Cheyne et al., 2009), and our chores and duties in everyday life (Carriere et al., 2008; McVay et al., 2009). The experience of mind wandering and its associated disruption in neurocognitive processing has not been assessed in BCS, and may provide valuable and novel insight into the cognitive complaints reported by BCS.

Given the prevalence and impact of mind wandering on our daily functioning, much research has been devoted to develop a measure that captures this ubiquitous experience and quantifies its frequency of occurrence. The most straightforward manner to investigate mind wandering is to directly ask participants to report their attentional state. This method of experience sampling has been used extensively in the literature in both experimental and observational studies (Smallwood et al., 2003; Christoff et al., 2009; Braboszcz and Delorme, 2011; Kam et al., 2011). Importantly, there is a high correspondence in the reported frequency of mind wandering between these two settings (McVay et al., 2009). In an experimental setting, participants are asked at unpredictable intervals to report their attentional state in the moment while they perform a task. This methodology has been used to demonstrate reliable and replicable differences in neurocognitive functioning between on-task and mind wandering states (Talairach and Tournoux, 1988; Smallwood et al., 2008; Kam et al., 2011, 2014; Kirschner et al., 2012). For instance, this self-report classification of attentional states has been associated with a systematic down-regulation of both sensory (Braboszcz and Delorme, 2011; Kam et al., 2011) and cognitive processing (Kam et al., 2014; Smallwood et al., 2008) during mind wandering states, as well as an up-regulation of activity in the brain's default mode network (Kirschner et al., 2012). Our current understanding of mind wandering and the neural correlates associated with this phenomenon allows us to consider ways in which this experience can be engaged in a non-normative manner in BCS.

The current study aimed to examine whether BCS who report persistent cognitive impairment following adjuvant chemotherapy for breast cancer show an abnormal pattern of sustained attention. To address this question, we measured both the frequency of mind wandering and the extent of cognitive processing of external stimulus as participants performed a sustained attention task. Throughout the task, we occasionally asked participants to report their attentional state as a way to quantify the frequency of mind wandering. We recorded their event-related potentials (ERP) during the task as an objective measure of the extent of cognitive processing of task-relevant stimulus engaged during periods of on-task and mind wandering. Specifically, the P300 ERP component reflects an attention-related cognitive process that involves stimulus evaluation and classification (Polich, 2009). Its amplitude indicates the intensity of neuronal activity reflecting the amount of attentional resources engaged, while its latency indicates the speed and duration of the neural process involved during task performance. Further, we also examined participants' electroencephalogram (EEG) at rest, as it has been linked to variations in cognitive task performance (Finnigan and Robertson, 2011; Stam et al., 2002) and has reliably differentiated healthy individuals from neurological and clinical populations, such as Alzheimer's disease and depression (Babiloni et al., 2013; Thibodeau et al., 2006). Resting EEG can be measured in terms of power within specific

frequency bands, which indexes the average magnitude of oscillation of electrical activity over a specified time range. Of relevance, the power of EEG activity during rest has been associated with activity within the default mode network (Britz et al., 2010; Laufs, 2008), a neural network that is generally more active during rest than task performance (Greicius et al., 2003; Li et al., 2002) and has been implicated in mind wandering (Christoff et al., 2009; Kirschner et al., 2012; Mason et al., 2007). Taken together, disruptions in resting EEG may indicate disturbances in neural activity underlying attentional processes in the absence of an external task.

We hypothesized that BCS would: (1) report higher levels of mind wandering, and (2) experience greater attenuation of cognitive processing during mind wandering in a sustained attention task, relative to healthy controls. To our knowledge, this is the first study to consider attention-related cognitive impairments in BCS from the perspective of the mind wandering phenomenon.

2. Methods

2.1. Participants

Two groups of participants were compared in this study: a group of breast cancer survivors (BCS, $n = 19$) who received adjuvant chemotherapy and a control group of healthy women (HC, $n = 12$). BCS were recruited through oncologist referrals and invitations via phone calls or emails. The eligibility criteria for the BCS group included women who were 40–65 years of age, reported cognitive deficits during or following chemotherapy, have completed chemotherapy and/or radiation treatment for stages I–IIIA breast cancer for at least 3 months within the last 3 years, and who were post-menopausal and were taking anti-hormone therapy. Exclusion criteria included women who had clinical conditions that may alter cognitive testing results (i.e., anxiety disorder, history of substance abuse or neurological disorder), were taking medications that negatively affect cognitive function (e.g., major tranquilizers or anticonvulsants), and reported greater than 90 min per week of moderate-to-vigorous physical activity within the last 6 months. HC were women recruited through public advertisements. They were 40–65 years of age, post-menopausal, and engaged in less than 150 min of moderate-to-vigorous exercises per week. The exclusion criteria regarding usual physical activity was included because BCS were recruited as part of a randomized controlled trial examining the impact of exercise on cognitive complaints following chemotherapy. Participants completed one test visit at the University of British Columbia, during which EEG was recorded at rest and during a sustained attention task. This study was approved by the Clinical Review Ethics Board at the University of British Columbia. All participants provided written informed consent.

2.2. Sustained attention task

The sustained-attention-to-response task (SART; Robertson et al., 1997) is a simple target detection task in which participants have to respond to a frequent non-target and withhold their response to a rare target. Successful performance on this task requires sustained attention, yet it makes minimal demands on other cognitive processes. Importantly, an error reflects not a failure on a single trial, but rather a failure in maintaining attention over time. This task has two major advantages. First, it has been extensively used in the mind wandering literature as the repetitive, monotonous nature of the task tends to naturally facilitate episodes of mind wandering (Christoff et al., 2009; Kam et al., 2011; Kirschner et al., 2012; Smallwood et al., 2004). Second, performance on this task correlates with our tendency to attentional failures in everyday life (Carriere et al., 2008; Robertson et al., 1997) reflecting the high ecological validity of this task.

2.2.1. Stimuli and paradigm

During the SART, a continuous stream of visual stimuli was presented at fixation. Participants were instructed to make a manual button press for frequently presented numbers (0–9), which we refer to as non-targets. They were to withhold their response when presented with the infrequent letter "X", which we refer to as targets.

Each target or non-target was presented for 500 ms followed by an interstimulus interval that varied between 400 and 600 ms. A task-irrelevant tone (2000 Hz) was then presented for 100 ms through an external speaker placed behind the participant directly along the vertical midline. Participants were informed that these probes were irrelevant to the task, and therefore they could ignore their presence with no decrement to task performance. While this task irrelevant tone was used in an earlier study to examine auditory attention in an undergraduate population, the neural response to this tone was not examined in this study as we have no theoretical rationale to examine peripheral sensory processing in the auditory domain in BCS. Following the tone was an inter-trial interval (ITI) that also randomly varied between 800 and 1000 ms. Within each block, the probability of target occurrence was quasi-randomized, with the constraints that: (i) one to two targets were presented during each block; (ii) for blocks having two targets, the targets would be separated by at least ten non-target events; and (iii) targets did not appear in the last 12 s prior to the end of a trial block. Participants completed up to 40 blocks and were permitted breaks in-between blocks, as requested. This task lasted approximately 60 min.

2.2.2. Attentional report

Our approach to determining whether or not participants were in a mind wandering state at any given moment was based on experience sampling. Experience sampling is a direct measure of mind wandering that relies on our ability to report whether or not our attention is focused on the task at hand (Smallwood et al., 2003, 2004). In this method, participants were instructed to verbally report their attentional state when prompted as either being on-task or mind wandering. To facilitate this, participants were provided with standardized definitions of these attentional states prior to testing; on-task states were defined as when one's attention is firmly directed towards the task, and mind wandering states were defined as when one's attention has drifted away from the task.

Attentional reports were recorded at the conclusion of each trial block by the investigator, and these reports were then used to sort event-related potentials (ERP) data based on on-task vs. mind wandering states. In order to maximize the variability of attentional states and minimize predictability of when an attentional report would be required, the duration of each trial block was randomly varied between 30 and 90 s, or 15–45 trials (Kam et al., 2011; Smallwood et al., 2008).

2.3. Task-induced electrophysiological data recording and processing

During SART performance, EEG was recorded from 64 active electrodes mounted on a cap in accordance to the International 10–20 system using a Biosemi Active-Two amplifier system. Two additional electrodes located over medial-parietal cortex (Common Mode Sense and Driven Right Leg) were used as ground electrodes. EEG data were recorded using a high-pass filter of 0.05 Hz, digitized on-line at a sampling rate of 256 Hz, and then referenced offline to the average of two mastoid electrodes. To

ensure proper eye fixation and allow for the removal of events associated with eye movement artifacts, vertical and horizontal electrooculograms (EOGs) were also recorded.

EEG data processing and analyses were performed using ERPLAB (http://erpinfo.org/erplab), a toolbox within MATLAB (2012a) used in conjunction with EEGLAB (Delorme and Makeig, 2004). Continuous data was segmented into −200–800 ms epochs time-locked to stimulus presentation. Offline artifact rejection was used to eliminate trials during which detectable eye movements and blinks occurred. Eye movements or muscle artifacts were automatically rejected from analysis, using the moving windows peak-to-peak option in ERPLAB, with amplitude thresholds customized for each participant (range: 150–300 μV). An average of 23% of the total number of trials in HC, and 27% in BCS, were rejected due to these signal artifacts. The percentage of trials rejected did not significantly differ between HC and BCS (p = .329), nor did they significantly differ between on-task and mind wandering states in both BCS (p = .796) and HC (p = .245). One participant in the BCS group was excluded from subsequent analyses, as she did not have enough data to generate reliable ERP averages. Data were then submitted to an IIR Buttersworth band-pass filter of 0.1–30 Hz. Quantification of ERP data was based on mean amplitude measured relative to a −200–0 ms pre-stimulus baseline, with specific time-windows of analyses centered on the components of interest as identified in the grand-averaged waveforms.

2.4. Resting electrophysiological data recording and processing

Immediately before the SART, we recorded participants' EEG as they were asked to sit still in the dimly lit room with their eyes closed for 3 min (Clementz et al., 1994; Sponheim et al., 1994, 2000). Resting EEG data were processed and analyzed using the EEGLAB toolbox (Delorme and Makeig, 2004) within MATLAB (2012a). Continuous data were digitally filtered using a high-pass filter offline at 0.5 Hz. Segments of data containing high amplitude or high frequency abnormalities (such as those associated with jaw clenching and coughs) were removed by visual inspection. Bad channels were also removed from subsequent analyses.

Independent component analysis (ICA) was used to correct for ocular artifacts. The extended ICA method was performed using the runica algorithm implemented within EEGLAB. Independent components reflecting horizontal and vertical eye movements were identified and removed from the data.

All participants were included in subsequent analyses as they had at least 30s of artifact-free EEG data (Lund et al., 1995). There were no significant differences in the average duration of artifact-free EEG data segments between the two groups (BCS: M = 183.89 s, SD = 17.56, HC: M = 191.08 s, SD = 10.65 s; p = .215). Only the first artifact-free 120 s of data in both groups of subjects were included in subsequent analyses, as this was the minimum duration of artifact-fact free data available for all subjects. The artifact-free data were then referenced to the common average, and segmented into non-overlapping 2.048 s epochs. A Fast-Fourier transform was applied using the spectopo function in EEGLAB for spectral decomposition. To normalize the distributions, a natural log transform was computed for all output EEG power values. Each participant's data were averaged across the epochs for each electrode, and the mean absolute power was computed for each of the following frequency bands: low Alpha (8–10 Hz), high Alpha (10–12 Hz), low Beta (12–20 Hz), and high Beta (20–30 Hz), as these frequency bands have been associated with mind wandering, (O'Connell et al., 2009) and the default mode network (Laufs et al., 2003; Mantini et al., 2007). EEG power values measured at individual electrodes were aggregated to create an average for the following regions: frontal (F7, F3, Fz, F4, F8), central (C3, Cz, C4), parietal (P7, P3, Pz, P4, P8), and temporal (FT7, T7, FT8, T8).

2.5. Outcome measures and statistical analyses

2.5.1. Attentional reports and behavioral performance

To assess group differences in sustained attention, the percentage of mind wandering reports was compared between BCS and HC. In terms of behavioral measures, we compared hit rates and commission error rates, as well as reaction times to non-targets preceding errors between the two groups. The hit rate (i.e., accurately responding to non-targets) indicates overall attentional performance in the SART, whereas the commission error rate (i.e., failure to withhold response to the infrequent targets) is considered to reflect a lapse in sustained attention (Robertson et al., 1997). We also examined overall reaction times and variability in reaction times.

2.5.2. Task-induced ERP measures

We assessed the P300 (or P3) ERP component as an index of the attention-related cognitive process engaged in response to the targets and non-targets presented during the SART by measuring its amplitude and latency. We compared both the overall P3 amplitude and latency measures in response to targets and non-targets between the BCS and HC groups. To compare the P3 responses between on-task and mind wandering states, we only included the six non-targets in our ERP averages that were presented in the 12 s preceding each on-task vs. mind wandering attentional report across the entire recording session (Kam et al., 2011, 2014; Kirschner et al., 2012; Smallwood et al., 2008). The P300 component in response to frequent non-targets occurring within this time period was averaged as a function of whether they preceded on-task or mind wandering reports, and separately for the BCS and HC groups.

2.5.3. Resting EEG measures

We assessed differences in EEG power at rest between the HC and BCS, across the four frequency bands and four regions. A functional interpretation of group differences in resting EEG power can be made in associating this measure with behavioral measures (Finnigan and Robertson, 2011; Stam et al., 2002). Accordingly, we examined the correlations between EEG power measured at rest and the behavioral performance during SART.

2.5.4. Statistical analyses

Univariate ANOVAs were conducted to examine group differences in behavioral performance, including reaction time and accuracy measures. Repeated-measures ANOVAs were conducted to examine group differences in ERPs and resting EEG power. Each omnibus ANOVA included a between-subject factor of Group (BCS, HC) and a covariate of Age. Additional factors included in each ANOVA are described below in their corresponding sections. Significant interaction effects were decomposed by additional ANOVAs. Post-hoc tests were carried out by independent samples t-tests or ANOVAs, adjusted for multiple comparisons using Bonferroni correction. When sphericity assumption was violated, Greenhouse–Geisser estimates were reported. All statistical analyses were conducted using Predictive Analytics Software 18.0 (Chicago, USA).

3. Results

3.1. Participants

Participants' demographic and clinical characteristics are presented in Table 1. The BCS group consisted of early stage breast cancer survivors, all of whom had received chemotherapy as part of breast cancer treatment and self-reported persistence cognitive

impairments up to 3 years following treatment. Preliminary analyses assessed potential differences between groups in demographic factors related to task performance, specifically age and education. Independent samples *t*-test revealed that HC were significantly older than BCS, therefore age was included as a covariate in subsequent ANOVAs.

3.2. Attentional reports

Participants completed an average of 38 trial blocks in the SART. BCS ($M = 57\%$, $SD = 16\%$) reported significantly higher levels of mind wandering relative to HC ($M = 39\%$, $SD = 15\%$; $t(29) = -2.93$, $p = .007$).

3.3. Behavioral performance

The descriptive measures of behavioral performance on the SART are reported in Table 2. In terms of overall reaction times in response to non-targets, BCS responded slower than HC; however this difference did not reach significance ($F(1,28) = 1.98$, $p = .170$). We also examined reaction times for trials preceding on-task and mind wandering reports. A similar pattern of reaction times between groups was observed during periods of on-task ($F(1,28) = 2.11$, $p = .158$) and mind wandering ($F(1,28) = 1.43$, $p = .242$).

Intra-individual variability in reaction times appeared to be greater in BCS relative to HC. This was confirmed by a significant main effect of Group ($F(1,28) = 7.25$, $p = .012$). Reaction time variability was also higher in BCS compared to HC during on-task episodes ($F(1,28) = 6.02$, $p = .021$) as well as mind wandering episodes ($F(1,28) = 4.71$, $p = .039$).

Overall hit rate of non-targets was significantly higher in HC compared to BCS ($F(1,28) = 7.59$, $p = .010$). While the same pattern was observed during periods of on-task ($F(1,28) = 8.93$, $p = .006$), this difference was not significant during periods of mind wandering ($F(1,28) = 2.63$, $p = .116$). Although commission error rates were numerically higher in BCS than HC, this difference was not significant ($F(1,28) = 0.20$, $p = .659$).

Table 1
Demographic and clinical characteristics of HC ($n = 12$) and BCS ($n = 19$).

	Healthy controls	Breast cancer survivors	*P* value
Age (SD)	59.3 (4.1)	52.4 (6.1)	.001
Level of education (*n*, %)			.135
Completed high school or some vocational training	1 (9)	3 (16)	
Some college or college graduate	4 (33)	12 (63)	
Post-graduate college or professional program or degree	7 (58)	4 (21)	
Clinical characteristics		*n* (%)	
Cancer stage			
I	–	0 (0)	
II	–	17 (89)	
III	–	2 (11)	
Surgery			
Lumpectomy/partial mastectomy	–	12 (63)	
Mastectomy	–	7 (37)	
Chemotherapy protocol[a]			
AC (all variants)	–	4 (21)	
DC	–	7 (37)	
FECD	–	8 (42)	
Radiation			
Yes	–	18 (95)	
No	–	1 (5)	
Months since treatment (SD)	–	11.3 (6.7)	

[a] AC, Doxorubicin and Cyclophosphamide; DC, Docetaxel and Cyclophosphamide; FEC, 5-Flourouracil, Epirubicin, Cyclophosphamide.

Table 2
Behavioral performance on the SART as a function of attentional states are shown separately for HC ($n = 12$) and BCS ($n = 19$). Standard deviations are presented in parentheses.

	Healthy controls	Breast cancer survivors
Reaction time measures (ms)		
RT to non-targets		
Overall	415 (41)	432 (57)
On task	409 (44)	428 (57)
Mind wandering	414 (47)	430 (67)
RT intra-individual variability		
Overall	82 (17)	103 (21)
On task	78 (20)	96 (25)
Mind wandering	78 (22)	106 (29)
Accuracy rates (%)		
Hit rate (non-targets)	99.11 (0.77)	94.18 (4.95)
Commission error rate (targets)	20.67 (7.63)	26.78 (16.06)

3.4. Task-induced ERP data

ERP waveforms are shown in Figs. 1 and 2. ERP data analyses focused a priori on the P3 response to the targets and non-targets beginning about 400 ms post-stimulus on midline channels. All ERP data analyses reported below were based on mean amplitude measures using repeated-measures ANOVAs, with specific time-windows of analyses centered on the peak of the P3 as identified in the HC and BCS grand-averaged waveforms. Repeated-measures ANOVAs included within-subject factors of stimulus type (targets, non-targets) and electrode location (Fz, FCz, Cz, CPz, Pz). The mean amplitudes and standard errors of the mean of the P3 response to both stimulus types across a 400–550 ms and 450–600 ms post-stimulus time window for HC and BCS respectively at electrode sites Fz, FCz, Cz, CPz, and Pz are shown in Table 3. Neither main effects of stimulus type nor electrode location were significant ($p > .30$). No interaction effects involving Group were significant ($p > .05$). Importantly, there was a significant main effect of Group ($F(1,27) = 4.54$, $p = .042$), with P3 amplitudes being lower for BCS compared to HC.

To examine group differences in the timing of the P3 response, we compared its peak latency, quantified as the most positive peak within a 400–600 ms time window. The main effects of stimulus type and electrode location were not significant ($p > .10$). The interaction between stimulus type and Group was also not significant ($F(1,27) = 1.94$, $p = .176$). Nevertheless, as we observed latency differences between the targets and non-targets averaged waveforms in Fig. 1, we ran exploratory analyses to examine this observed group difference by conducting ANOVAs separately for targets and non-targets. P3 latencies were significantly longer in BCS relative to HC for non-targets ($F(1,27) = 8.31$, $p = .008$), but this difference was not significant for targets ($F(1,27) = 0.42$, $p = .522$).

We further examined the P3 response to non-targets as a function of whether the stimulus occurred during on-task or mind wandering states. Thus, repeated-measures ANOVAs included an additional factor of attentional states (on task vs. mind wandering). The mean amplitudes and standard errors of the mean of the P3 response to both stimulus types across a 400–550 ms post-stimulus time window for both HC and BCS respectively at electrode sites Fz, FCz, Cz, CPz, and Pz are shown in Table 4. Neither main effects of attentional states nor electrode location were significant ($p > .70$). No interaction effects involving Group were significant ($p > .40$). There was a significant main effect of Group ($F(1,27) = 5.38$, $p = .028$), with lower P3 amplitudes found in BCS compared to HC.

3.5. Resting EEG data

The average EEG power at each region and frequency band for each of the two subject groups is presented in Fig. 3. One participant

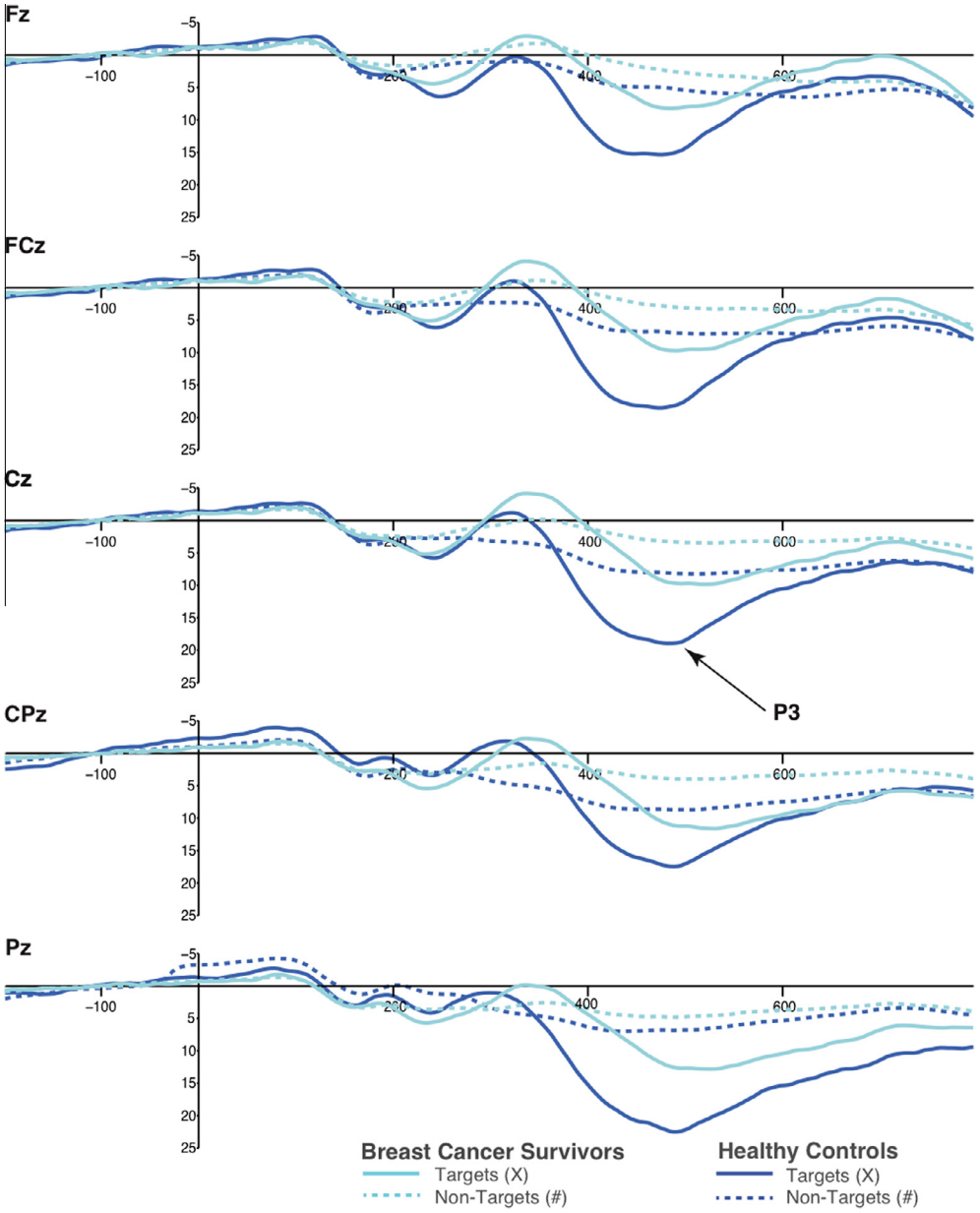

Fig. 1. P3 component time-locked to all targets and non-targets in the SART. P3 recorded at midline separately for targets (solid lines) and non-targets (dotted lines) for both breast cancer survivors (light blue lines) and healthy controls (dark blue lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in the BCS group did not have EEG data at rest due to technical errors at the time of recording. Repeated-measures ANOVAs included within-subject factors of frequency band (low alpha, high alpha, low beta, high beta) and regions (frontal, central, parietal, temporal). There were no significant main effects of frequency band and regions ($p > .30$), nor were there significant two-way interaction effects involving Group ($p > .30$). Importantly, the frequency band by region by Group interaction was significant ($F(9,243) = 3.28$, $p = .011$). To follow up this three-way interaction, we conducted additional ANOVAs to examine the relationship between region and Group separately at each frequency band. There was a significant region by Group interaction only at low alpha ($F(3,78) = 4.50$, $p = .006$). Post-hoc analyses revealed a significant effect of Group at the frontal region only ($F(1,26) = 5.16$, $p = .032$), with BCS displaying higher EEG power than HC.

In order to make functional interpretations of EEG power at rest, we ran correlations to examine the relationship between EEG power at rest and behavioral performance on the subsequently implemented sustained attention task (i.e.,: SART). We found a near-significant correlation between frontal low alpha power and reaction times to non-targets ($r(31) = .33$, $p = .076$), suggesting that higher alpha power at rest is associated with overall slower reaction times in the subsequently administered SART.

4. Discussion

The current study examined whether women who have undergone adjuvant chemotherapy for breast cancer and self-report persistent problems in cognitive function up to three years following completion of treatment demonstrate altered ability to maintain attention relative to healthy controls. Our findings revealed that BCS have a higher propensity to mind wander than HC. In terms of behavioral performance in the sustained-attention task, they

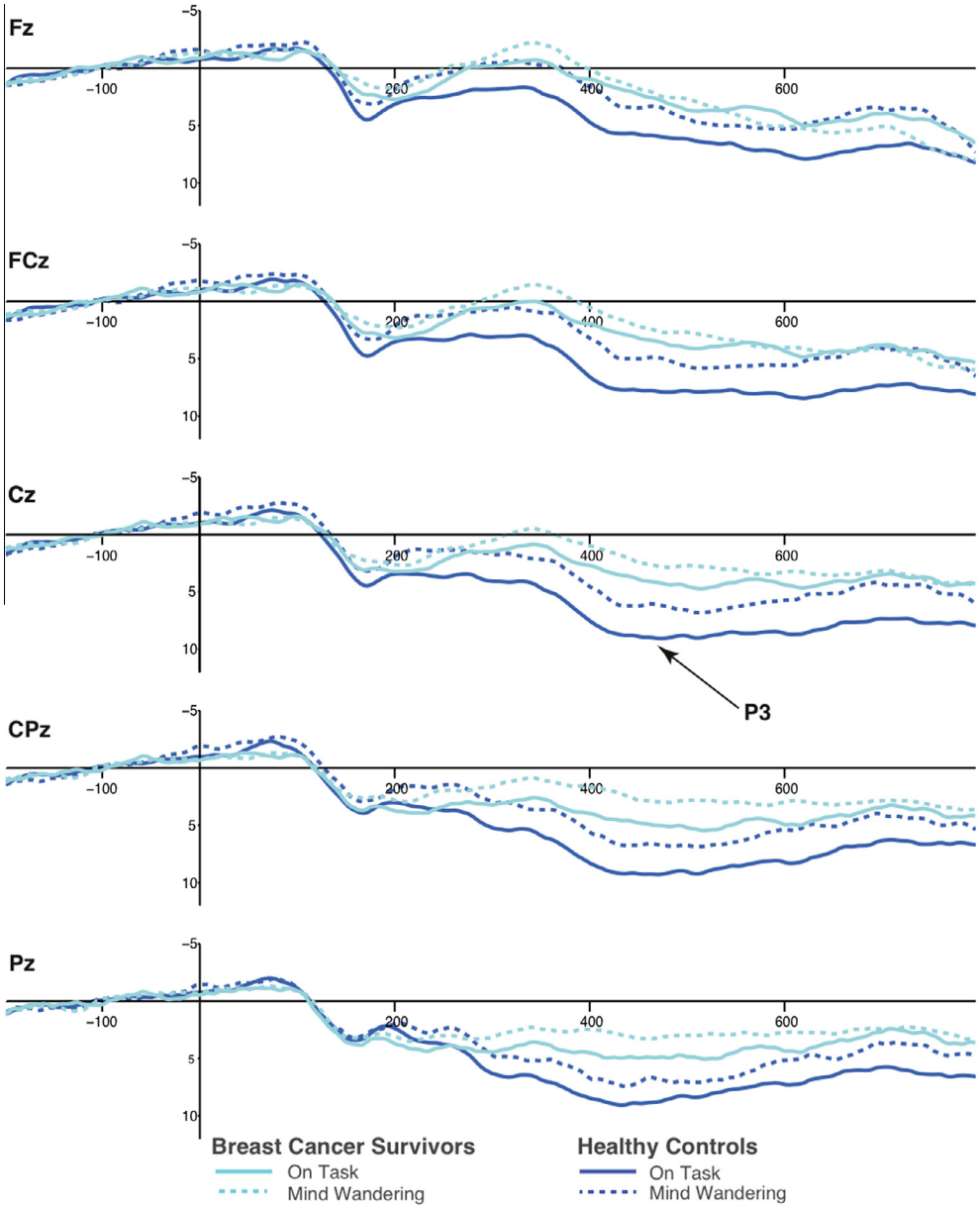

Fig. 2. P3 component time-locked to non-targets in the SART as a function of attentional states. Non-targets (or numbers) preceding attentional report recorded at midline were averaged separately for on-task (solid lines) and mind wandering reports (dotted lines) for both breast cancer survivors (light blue lines) and healthy controls (dark blue lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

showed greater intra-individual variability in reaction time, as well as a lower overall hit rate, than HC. In terms of neural response, the overall P3 amplitude was lower in BCS relative to HC; however this pattern was not significantly modulated by attentional states. Further, overall P3 latencies to non-targets were longer in BCS compared to HC. BCS also displayed higher power at low alpha than HC at rest, a finding that corresponds with slower reaction time. Taken together, these findings suggest that BCS are associated with an abnormal pattern of sustained attention compared to HC.

First, we found that BCS reported higher levels of mind wandering than HC when they were performing a laboratory task, which indicates a higher degree of distractibility. Yet, they showed greater neural activity when they were resting in a frequency band that is associated with the default mode network (Laufs et al., 2003), a neural network that shows greater activation during rest than task performance (Greicius et al., 2003; Li et al., 2002), and has been associated with mind wandering (Christoff et al., 2009; Kirschner et al., 2012; Mason et al., 2007). This reflects a hyperactive internally-oriented attentional mode in BCS. Given this pair of results, our findings may indicate that BCS more frequently attend to inner thoughts. Previous studies indicate that individuals tend to think about their current concerns when mind wandering (Klinger and Cox, 1987). This suggests that BCS are more likely to be engaged with their thoughts associated with current concerns whether or not they are performing an external task. This is consistent with past findings in which BCS report attention or concentration problems in their daily life (Kreukels et al., 2006; Schagen et al., 1999; van Dam et al., 1998). Although it remains to be determined whether this higher propensity to mind wander in BCS originates from chemotherapy itself or their concerns as a consequence of cancer diagnosis and treatment, this finding suggests

Table 3
Mean amplitudes and latencies (and their standard deviations) for P3 component time-locked to targets and non-targets are shown separately for HC (n = 12) and BCS (n = 18).

	Healthy controls		Breast cancer survivors	
	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)
Targets				
Fz	13.27 (7.15)	503 (79)	6.89 (6.91)	524 (67)
FCz	15.83 (9.81)	479 (67)	8.29 (6.65)	526 (69)
Cz	15.94 (11.01)	496 (75)	8.39 (6.96)	507 (68)
CPz	14.13 (12.29)	493 (77)	9.97 (6.22)	509 (66)
Pz	19.01 (15.66)	481 (70)	11.34 (5.26)	486 (69)
Non-targets				
Fz	4.59 (3.81)	473 (43)	2.52 (4.34)	500 (38)
FCz	6.30 (3.85)	471 (40)	2.82 (3.64)	499 (44)
Cz	7.45 (4.07)	483 (59)	3.10 (3.55)	519 (48)
CPz	8.19 (3.86)	485 (44)	3.70 (3.08)	526 (48)
Pz	4.64 (6.62)	494 (56)	4.50 (4.64)	525 (48)

Table 4
Mean amplitudes and latencies (and their standard deviations) for P3 component time-locked to non-targets as a function of attentional states are shown separately for HC (n = 12) and BCS (n = 18).

	Healthy controls		Breast cancer survivors	
	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)
On-task				
Fz	5.51 (4.25)	462 (61)	2.71 (4.48)	511 (69)
FCz	7.31 (4.04)	492 (66)	3.37 (4.22)	503 (70)
Cz	8.36 (4.29)	487 (56)	3.98 (3.91)	491 (67)
CPz	8.81 (4.03)	489 (71)	4.88 (3.09)	488 (61)
Pz	8.54 (2.53)	484 (65)	4.84 (2.52)	474 (53)
Mind wandering				
Fz	3.10 (5.43)	507 (58)	2.22 (4.59)	541 (65)
FCz	4.54 (5.53)	498 (63)	2.30 (3.47)	537 (66)
Cz	5.70 (5.56)	494 (68)	2.38 (3.58)	542 (71)
CPz	6.29 (5.37)	487 (60)	2.63 (2.94)	527 (74)
Pz	6.83 (4.39)	468 (63)	2.93 (2.38)	510 (74)

that an objective laboratory measure of attention can correspond with a self-report measure of inability to focus attention in their daily life.

BCS also showed disruptions in both behavioral and neural responses engaged during task performance relative to HC; particularly, lower accuracy rate as well as reduced overall amplitude of the P3 component. These findings suggest less attentional resources were allocated to task-relevant information. The overall reduced P3 component in BCS replicates previous findings by Kreukels et al. (2005, 2008a,b). In previous studies, an attenuation of cognitive response during mind wandering found in healthy individuals has been interpreted as reduced attentional resources allocation to the external environment (Barron et al., 2011; O'Connell et al., 2009; Smallwood et al., 2008). While we did not observe attentional state modulations of the P3 component, Fig. 2 indicates that the P3 amplitude in BCS during on-task is lower than the P3 amplitude in HC during mind wandering. This comparison suggests that even when BCS are focused on the task-at-hand, they may only be exerting a similar reduced amount of resources as HC when they mind wander. In terms of attentional resource engagement as indexed by P3 amplitude, our data suggest that the focused attentional state of BCS is not unlike the mind wandering brain of HC.

Another key finding was the slower processing speed in BCS. Longer P3 latency was observed in BCS relative to HC, reflecting slower information processing speed during task performance. This aligns with past findings of longer P3 latencies in BCS who self-report cognitive impairments but not in BCS who did not report cognitive impairments (Kreukels et al., 2008a). Despite longer P3 latency in BCS in our study however, we did not find significant group differences in reaction time. This is consistent with previous findings indicating that SART reaction time is insensitive to attentional state modulations (Kam et al., 2011; Smallwood et al., 2008). The absence of attentional state and group differences in reaction time in the current study highlights the importance and utility of ERP measures in examining the underlying neural mechanism that may not manifest in traditional behavioral measures. Interestingly, there was greater intra-individual variability in reaction time in BCS, suggesting that while BCS did not take longer to respond, they showed more trial-by-trial variability. This particular behavioral index has been proposed to index attentional lapses in task performance (Sonuga-Barke and Castellanos, 2007). In fact, it has been associated with activity in the default mode network (Weissman et al., 2006). Based on the tight link between mind wandering and the default mode network (Christoff et al., 2009; Mason et al., 2007), our data showed that engaging in our internal thoughts may be manifested as unstable or more variable behavior in response to the external environment.

Given our methodology, the subjective nature of the experience sampling approach calls into question its validity as a measure of attentional states. Of importance, compared to questionnaires or behavioral indices, our measure of mind wandering yields multiple measurements thereby enhancing reliability. The direct report of immediate experience also minimizes inaccuracy associated with retrospective recall. While this methodology has been extensively used in the mind wandering literature, two concerns commonly arise. First, participants were asked to verbally report their attentional state. While the verbal report of attentional states may have increased the risk of demand characteristics thereby potentially affecting the validity of the reports, the proportion of on-task vs. mind wandering reports have been consistent across studies in healthy individuals regardless of the methodology used, whether participants provided a response verbally to the experimenter or through button press (Christoff et al., 2009; Kam et al., 2011; Kirschner et al., 2012; Smallwood et al., 2008). Second, the choice of averaging experimental trials within 12 s preceding attentional report may seem arbitrary, but was chosen for several reasons. The time course of attentional fluctuations between on-task and mind wandering states approximate this time window (Christoff et al., 2009; Smallwood et al., 2003). Of relevance, this is also a time window used previously with ERP data that is designed to maximize the number of events that can be included in the ERP averages while still maintaining a reasonable fidelity to the actual attentional report (Christoff et al., 2009; Kam et al., 2011; Kirschner et al., 2012; Smallwood et al., 2008). That is, as the time window increases, the signal-to-noise ratio of the ERP averages improves, but the validity of the attentional report for individual trials decreases. Briefly, the experience sampling approach, as used in the current study, has shown to be a valuable laboratory measure of sustained attention.

Our findings should be considered with the following limitations. One concern is that we lacked a comparison group of BCS who did not undergo chemotherapy. Therefore we are unable to definitively determine whether the attentional impairments observed in BCS was a consequence of the disease process, the diagnosis, or the chemotherapeutic agents. Notably, one study comparing BCS who did and did not receive chemotherapy still observed cognitive impairments as indexed by reduced P3 amplitude in the group who did receive chemotherapy (Kreukels et al., 2005). Further, we do not have baseline data that would allow us to examine cognitive performance prior to or immediately following chemotherapy. These data would have allowed us to determine whether the cognitive deficits we observed at testing indicate

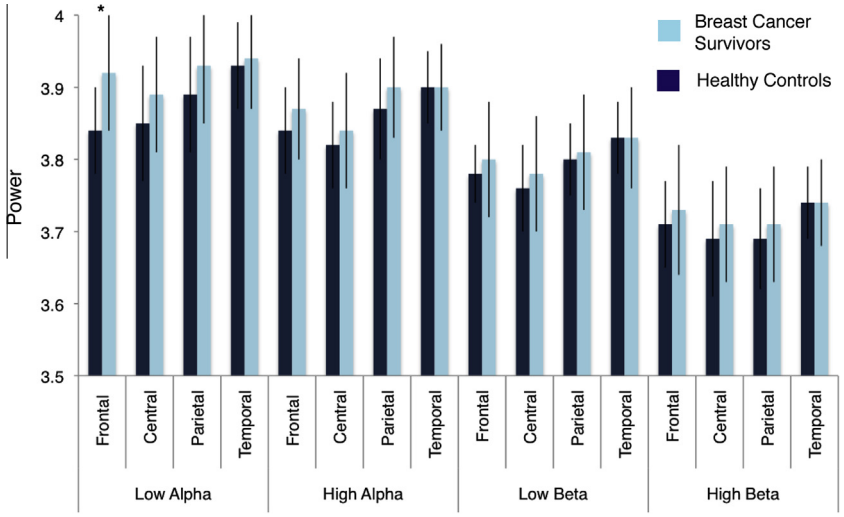

Fig. 3. Mean resting EEG power by region and frequency band. EEG power values were averaged separately for four regions at low alpha, high alpha, low beta and high beta bands for both breast cancer survivors (light blue bars) and healthy controls (dark blue bars). Error bars indicate standard deviations. $^{*}p < .05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

persistent deterioration or partial recovery. A related issue concerns the lack of a BCS group who underwent chemotherapy but did not experience cognitive problems. This comparison group may allow us to examine factors that increase the risk of developing cognitive deficits in BCS treated with chemotherapy. Moreover, our study recruitment criteria limited the BCS to women who were post-menopausal at time of entry into the study and HC who were also post-menopausal and not taking hormone replacement therapy. While setting these restrictions limit the generalizability of our findings, they also allow us to avoid potential confounding effects of hormones on cognitive functions (Sherwin and Tulandi, 1996). Finally, functional interpretations of resting EEG activity should be considered with caution given such activity was recorded in the absence of an external task. While additional research is necessary in order to accurately interpret changes in neural activity at rest, this particular measure provides a promising way to reveal abnormal spontaneous fluctuations in neural activity in patient populations and detect group differences.

4.1. Conclusion

In conclusion, BCS who self-report cognitive deficits up to 3 years following adjuvant chemotherapy displayed an abnormal pattern of sustained attention. Using a non-traditional measure of attention, we found that BCS have a higher propensity to mind wander away from task-relevant information, which suggests a greater propensity for their own thoughts to intrude on their focus on the task-at-hand. Importantly, they not only show similar attentional disruptions as studies using more traditional measures of attention but their focused level of attention-related cognitive functioning parallels the level of cognitive functioning during mind wandering in healthy postmenopausal women. These findings highlight the utility of a task-related attention measure as a novel tool for assessing subjective attention complaints. In fact, this abnormal pattern of attentional fluctuations between on-task and mind wandering states over time may be an important and heretofore underappreciated functional marker of chemotherapy-related cognitive impairments. Given the impact of cognitive problems on daily functioning and quality of life, future research may benefit from considering the neural mechanism underlying these problems from the perspective of sustained attention.

Acknowledgements

This study was funded by a grant from the Canadian Breast Cancer Foundation – British Columbia/Yukon. The funding source had no involvement in study design, data collection, analysis and interpretation, and the writing of the manuscript. JWYK was supported by the Natural Sciences and Engineering Research Council. Thank you to Tiffany Moore, Sarah Neil, Amy Kirkham, Kortni Peill, Lindsay Nagamatsu and Chelsea Eades for assistance with data collection. We also thank all our participants for their time and participation in the study. *Conflict of interest:* None of the authors have potential conflicts of interest to be disclosed.

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