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Neurocognitive efficiency in breast cancer survivorship: A performance monitoring ERP study

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ABSTRACT

Breast cancer diagnosis and treatment can lead to longer term cognitive and emotional vulnerability, making the ability to efficiently adapt to setbacks critical. Whilst cancer-related cognitive impairments (CRCI) are often reported amongst breast cancer survivors, investigation into the capacity to efficiently process errors is limited. The present study investigated the neurocognitive correlates of cognitive-control related performance monitoring, an important function influencing behavioural adjustment to mistakes. 62 participants (30 Breast Cancer Survivors, 32 Non-Cancer) completed a modified flanker task designed to challenge response inhibition as we measured neurocognitive indices of performance monitoring (ERN, the error-related negativity; CRN, the correct-response negativity; Pe, the error positivity). Findings indicated a blunted CRN and larger ΔERN in the breast cancer survivors compared to the non-cancer group, in the absence of performance effects. This was followed by a larger Pe in the breast cancer survivors' group, indicating an exaggerated performance monitoring response. For women affected by breast cancer, findings suggest an early disrupted neural response to monitoring cognitive performance, followed by the requirement for more effortful processing in the conscious response to errors, indicating deficits in neurocognitive efficiency. These findings have important implications for developing cognitive rehabilitation programmes for breast cancer survivors affected by cognitive dysfunction to assist in the monitoring and adjustment of performance required to meet established goals in the face of adversity.

1. Introduction

Amongst women, breast cancer is the most commonly diagnosed and leading cause of cancer death worldwide with increasing incidence (Bray et al., 2018). Nevertheless, the improvement of medical treatment has meant that significantly more women now survive breast cancer. In recent years this has prompted researchers to investigate the long-term side effects of cancer treatment and its resulting impact on survivors' quality of life.

The acknowledgement of cancer-related cognitive impairments (CRCIs) is now well established across the literature surrounding cancer survivorship. Whilst research indicates that the majority of breast cancer patients are affected by cognitive deficits during active treatment, longitudinal studies now indicate that a significant proportion of survivors report problems with cognition for up to 20 years post treatment (Wefel et al., 2010; Koppelmans et al., 2012). Originally coined 'chemobrain', the presence of such impairments was initially thought to derive solely from the neurotoxic effects of chemotherapy, however, increasingly this notion is disputed. Although it is clear that chemotherapy may play a large role in impacting cognitive function, it is becoming evident that it is not the sole contributing factor (see, Ahles and Root, 2018, for a review). This complication partly arises from the multiple modalities in which breast cancer is treated, making it difficult to isolate the most critical components that affect cognition. For instance, studies now show that hormonal therapies such as tamoxifen and aromatase inhibitors, which decrease estrogen levels in the body, may be a contributive factor (Castellon et al., 2004; Schilder et al., 2010). Conjointly, whilst radiotherapy is considered localized, it induces chronic fatigue, a systematic immune response and possible cognitive deficits (Shibayama et al., 2014). Moreover, cancer treatment can interact with multiple other factors including those which are predisposed (genetic, sociodemographic, cancer type) and those that can be modified (physiological, psychological, allostatic load and lifestyle). Indeed a number of biological theories surrounding potential mechanisms for cognitive

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decline in cancer are also emerging including inflammation (Ganz et al., 2013) and the predictive value of allostatic load (McEwen, 2015).

Critically for survivors it is important to understand to what extent cancer treatments can impact brain structure and function, which cognitive processes are most likely to be affected, and how such changes are manageable. Thus far, objective performance-based research has primarily furthered our understanding of CRCI in breast cancer. Performance-based neuropsychological testing has typically indicated cognitive dysfunction in the domains of attention, working memory, processing speed and learning and memory (see Ahles and Root, 2018 & Lange et al., 2019 for reviews). Nevertheless, a comprehensive understanding of precisely which cognitive functions are typically impaired, and which, if any, are likely to be unaffected, is yet to be determined (Horowitz et al., 2018). Indeed, the cognitive deficits reported on standard neuropsychological tests are often subtle. At the same time, however, survivors commonly self-report functional impairments, leading to small correlations between objective and subjective CRCI measures (Hutchinson et al., 2012; Costa and Fardell, 2019). Frequently survivors report difficulty returning to and maintaining performance at work and further describe the detrimental impact that cognitive deficits can have on social relationships and feelings of self-confidence (Von Ah et al., 2013; Selamat et al., 2014). This disparity may, in part, be due to the emphasis on standardized neuropsychological measures that were originally designed to assess impairment in patients with overt neurological injuries or disease, and thus may lack the nuance associated with cognitive decline in cancer patients (Ahles and Root, 2018). Understandably, it follows that there are minimal treatments for CRCIs available to survivors (Denlinger et al., 2014) and patients often report that the presence of such deficits are downplayed by the medical community (Selamat et al., 2014).

Neuroscientific approaches have the potential to facilitate our understanding of CRCIs and help reconcile seeming disagreements between extant behavioural and self-report measures. Structural studies indicate multiple changes in density of grey matter, integrity of white matter and volume in anterior/prefrontal regions (see, Andryszak et al., 2017, for a review) and functional imaging studies indicating task-specific hypoactivation and hyperactivation of various brain regions (Horowitz et al., 2018). McDonald and colleagues found prefrontal hyperactivation and more distributed activation patterns involved in working memory performance during an n-back task in breast cancer survivors relative to controls (McDonald et al., 2012). Increased prefrontal activation during task performance coupled with decreased white matter integrity has also been reported, even prior to the start of treatment (Menning et al., 2015), as well as after systemic treatment (Menning et al., 2018). Together, these findings are considered to reflect neural compensatory mechanisms, indicating deficits in neurocognitive efficiency, with increased recruitment of additional regions necessary to reach levels of premorbid cognitive effectiveness. Importantly, these neural differences are found in the absence of performance differences between groups, suggesting that reduced neurocognitive efficiency is coupled with more effortful processing required for breast cancer patients to function effectively to achieve the same level of performance as non-cancer controls (cf. Berggren and Derakshan, 2013; Ansari and Derakshan, 2011).

Few studies to date have used electroencephalography (EEG) to assess neural alterations in cognitive performance of breast cancer survivors. Studies have focused on the amplitude and latency of the P3, an event-related brain potential (ERP) marker of the evaluation/categorization of stimuli held in working memory. One study showed a reduced P3 amplitude during an oddball task in breast cancer survivors treated with chemotherapy relative to those not treated with chemotherapy (Kreukels et al., 2008). Similarly, Kam et al. (2016) found reduced P3 amplitude to task relevant stimuli in breast cancer survivors relative to healthy controls in a sustained attention task. Cognitive impairments in verbal memory as well as reduced memory accuracy were documented recently by Wirkner et al. (2017), where breast cancer survivors also showed reductions in the late window of the LPP (Late Positive Potential) in relation to unpleasant stimuli. Overall, findings indicate disruptions in neural mechanisms of attention and memory for breast cancer survivors.

1.1. The current investigation

Given the lack of ERP research in the area of CRCIs and the ambiguity across the literature in identifying the exact etiology and underlying mechanisms at work, it follows that there is scope to investigate other ERP components to better our understanding of deficits in neurocognitive efficiency in breast cancer survivors, as a means to build more efficacious interventions targeting this vulnerability. As outlined, cognitive dysfunction in the form of attentional and working memory lapses are commonly reported in the breast cancer population. This is problematic for everyday life in that it interferes with functioning across a variety of tasks, leaving survivors more prone to making cognitive errors. This may interfere not only with work ability and quality of life, but may result in reduced treatment compliance and disease progression (Horowitz et al., 2018). Moreover, it is well documented that cognitive control related inefficiency is associated with increased vulnerability to emotional disorders (Eysenck et al., 2007; Dolcos et al., 2019). Given that breast cancer survivors are a high-risk population for clinical levels of emotional distress (Pitman et al., 2018; Wang et al., 2020), it is important to understand how cognitive-control related processes are affected by diagnosis and treatment. Whilst cognitive control related deficits are increasingly investigated in breast cancer, numerous processes are yet to be researched. Indeed it is well documented that cognitive control involves several related yet dissociable processes including working memory, conflict error and detection set-shifting, abstract thought and reasoning, inhibition of pre-potent responses and the representation of rules and context (Parro et al., 2018). Accordingly, we decided to investigate neurocognitive efficiency through the neural correlates of cognitive-control related error monitoring, a function that is critical in behavioural adjustment to maintain task performance. Cognitive control relies on engaging top-down mechanisms to regulate attention towards task relevant information and inhibiting task irrelevant information, and as such plays a critical role in monitoring and orienting behavioural response to errors (Miller and Cohen, 2001; Eysenck et al., 2007). The mechanisms through which the brain detects and responds to errors, particularly in clinical populations, has become one of the fastest growing research areas in the field of neuroscience (Schroder and Moser, 2014; see Gehring et al., 2012, & Gehring et al., 2018, for reviews). Neuroimaging studies predominantly implicate regions of the anterior cingulate cortex (ACC; particularly the dorsal subdivision midcingulate cortex, MCC) and prefrontal cortex (PFC) in error monitoring and regulating necessary behavioural adjustments to maintain or improve performance on trials following mistakes (Hester et al., 2009).

The most widely measured neural index of error processing is the error related negativity (ERN), a negative ERP which reaches peak amplitude within 50-100 ms following an error response in basic reaction-time tasks such as the flanker or go/no-go tasks (Gehring et al., 1993). Broadly, the ERN is believed to index cognitive control-related error monitoring involved in signaling the need for implementing cognitive control functions when performance has broken down (Gehring et al., 2012). Following correct trials, there is also a smaller negativity referred to as the correct response negativity (CRN; Ford, 1999) which has a comparable morphology and source as the ERN. It has been proposed that the ERN and CRN reflect the same functional process, namely response monitoring (Vidal et al., 2000). Indeed, in order to reach our goals, our actions do not only have to be adjusted if erroneous, but they have to be continually evaluated also, even if correct (Hoffmann and Falkenstein, 2012). The ERN is followed by the error positivity (Pe) component, a positive ERP with a centroparietal topography which reaches maximum amplitude between 200 and 400 ms after an

erroneous response. Whereas the ERN is considered to reflect a more general conflict signal (Hughes and Yeung, 2011), it has been hypothesized that the Pe may either reflect the conscious awareness of an error, the affective response to an error and the adaptation of response strategies following an error, disassociating these two components (Schroder et al., 2013). Correspondingly, because the ERN implicates the dACC/MCC which is considered to be a hub for integrating emotional and cognitive information, it has been suggested that the ERN may represent an index of cognition-emotion interaction (Moser, 2017). Several studies show that experimental manipulations that aim to increase the affective or motivational significance of errors seem to produce a greater ERN (Hajcak et al., 2005; Riesel et al., 2012). As such the ERN may indicate a combination of cognitive and affective/motivational processes involved in neurocognitive efficiency.

To date a number of studies have investigated the ERN/Pe relationship in psychopathology, specifically in depression, anxiety disorders and substance abuse, with findings indicating abnormal response monitoring for such disorders (see Olvet and Hajcak, 2008 and Pasion and Barbosa, 2019, for reviews). Whilst promising findings continue to emerge in the field of psychopathology, the ERN and Pe have yet to be investigated in relation to CRCI in breast cancer survivors. Having the cognitive capacity to adapt to failures and setbacks seems particularly pertinent to breast cancer survivors, a population with known cognitive and emotional deficits who often struggle with feelings of self-efficacy post treatment, potentially hindering their ability to function effectively at both work and home. To this end, we examined the neurocognitive correlates of error processing by investigating the ERN and Pe components during a flanker task specifically designed to challenge cognitive-control related error monitoring. In addition, we measured levels of emotional vulnerability, perceived cognitive functioning, and fatigue to explore their relationship with neural processing and control for potential confounds.

In light of the aforementioned studies on compensatory mechanisms at work in breast cancer survivors, we predicted that breast cancer survivors would show a greater ERN and Pe compared to non-cancer controls in the absence of performance effects, indicating the requirement for more effortful processing in error monitoring.

2. Method

2.1. Participants

The study was advertised through the Birkbeck Centre for Building Resilience in Breast Cancer (BRiC) and various breast cancer support networks via social media platforms such as Facebook and Twitter. In total, 62 participants (30 Breast Cancer Survivors, 32 Non-Cancer) were recruited for the study, with funding limits and time restraints largely determining our stop rule for data collection. Participants were required to have had a diagnosis of primary breast cancer and have had chemotherapy as part of their treatment plan. Those with metastatic cancer were not included in the current study and participants must have finished active treatment to partake. Participants received a fee of £25 upon completion of the study. For participant demographics, clinical characteristics and psychiatric history see Table 1. Ethical approval was granted by the departmental ethics committee as well as from the ESRC panel at Birkbeck College University of London.

2.2. Materials and experimental tasks

2.2.1. Flanker task

Participants completed a modified letter version of the Eriksen Flanker task (Eriksen & Eriksen, 1974). Participants were presented with a string of five letters in which the target (the centre letter) was either congruent (e.g. MMMMM or NNNNN) or incongruent (e.g. MMNMM or NNMNN) which included distractor letters. Participants were instructed to respond by clicking the right or left side of the computer mouse based

Table 1
participant demographics, clinical characteristics, and psychiatric history.

	Breast cancer ($n = 30$)		Non-cancer ($n = 32$)		P
Age (years)[a]	48 (8.47)		44 (8.94)		.07
Age at diagnosis (years)	43 (7.54)		–		–
Time since diagnosis (months)	56 (46.85)				
	No. (%)				
Education					.07
GCSE's	5	(16.7)	1	(3.1)	
A-Levels	5	(16.7)	5	(15.6)	
Undergraduate	10	(33.3)	20	(62.5)	
Postgraduate	10	(33.3)	6	(18.8)	
Ethnic origin					.3
White	27	(90)	23	(71.9)	
Black	–		1	(3.1)	
Asian	1	(3.3)	3	(9.4)	
Mixed race	1	(3.3)	4	(12.5)	
Other	1	(3.3)	1	(3.1)	
Employment status					.89
Full time	13	(43.3)	15	(46.9)	
Part time	7	(23.3)	8	(25)	
Unemployed	3	(10)	2	(6.3)	
Maternity leave	1	(3.3)	–	–	
Retired	2	(6.7)	1	(3.1)	
Volunteering	1	(3.3)	–	–	
Student	1	(3.3)	1	(3.1)	
Sick leave	–	–	1	(3.1)	
Self employed	1	(3.3)	2	(6.3)	
Other	1	(3.3)	2	(6.3)	
Marital status[b]					.001*
Married	19	(63.3)	5	(15.6)	
Divorced	2	(6.7)	4	(12.5)	
Single	4	(13.3)	16	(50)	
Separated	–	–	2	(6.3)	
Cohabiting with partner	5	(16.7)	2	(6.3)	
Other	–	–	2	(6.3)	
Current psychological medication					.91
Yes	5	(16.7)	5	(15.6)	
No	25	(83.3)	27	(84.4)	
Previous psychological condition					.07
Yes	9	(30)	17	(53.1)	
No	21	(70)	15	(46.9)	
Alcohol intake[c]					.99
None	6	(20)	6	(18.8)	
1–5 units	13	(43.3)	14	(43.8)	
6–9 units	3	(10)	3	(9.4)	
10–14 units	5	(16.7)	5	(15.6)	
14+ units	2	(6.7)	3	(9.4)	
Diagnosis					
Primary	30	(100)	–	–	–
Secondary	–	–	–	–	
Grade of cancer					
Low	2	(6.7)	–	–	–
Moderate	9	(30)	–	–	–
High	19	(63.3)	–	–	–
Chemotherapy					
Yes	30	(100)	–	–	–
Radiotherapy					
Yes	28	(93.3)	–	–	–
Surgery type					
Mastectomy	9	(30)	–	–	–
Lumpectomy	16	(53.3)	–	–	–
Both	5	(16.7)			
Endocrine therapy[d]					
Yes	24	(80)	–	–	–

[a] Values indicate means and standard deviations unless indicated otherwise.
[b] One participant did not disclose their marital status.
[c] Two participants did not disclose their alcohol intake.
[d] One participant did not disclose whether they were currently taking endocrine therapy.
* Significant between-group difference, $P = .05$.

on the instructions they were presented with at the beginning of each block. For example, during the first block, participants were instructed to responded with a left sided mouse click if the target letter was M, and a right click if the target letter was N. Flanking letters were presented 35 ms prior to target letter presentation and remained on the screen for a further 100 ms (total trial time 135 ms). During a variable inter-trial interval (1200–1700 ms) between each trial, a fixation cross was presented. Stimuli were presented via the software package *E*-Prime to control the presentation and timing of stimuli along with determination of response accuracy and measurement of reaction times. The task included 480 trials grouped into 12 blocks of 40 trials. Across the task, 50% of trials were congruent and 50% incongruent. Characters were presented in a standard white font on a black background and subtended 1.38° of the visual angle vertically and 9.28° horizontally. To ensure elicitation of a sufficient number of errors for reliable ERN analysis, (Olvet and Hajcak, 2009) the letters used for trial stimuli differed across blocks (Block 1 & 2: 'M' and 'N", Block 3 & 4: 'F' and 'E', Block 5 & 6: 'O' and 'Q', Block 7 & 8: 'T' and 'I', Block 9 & 10: 'V' and 'U' Block 11 & 12: 'P' and 'R'. Additionally, mouse button-letter response mappings were reversed within each block pair (e.g. a M target for Block 1 required a left click response, whereas a M target for Block 2 required a right click response). Accuracy and speed were equally emphasized to the participant. No performance feedback was given across the task. The task was designed on E-Prime and was presented on an Asus VG248QE 24 in. LCD Monitor with a resolution of 1920 × 1080 and a refresh rate of 60 Hz.

2.2.2. Questionnaires

Participants completed the following questionnaires:

The Ruminative Response Scale (Treynor et al., 2003): A 22-item scale with a Likert scale ranging from 1 (*"almost never"*) to 4 (*"almost always"*), with higher scores indicating higher levels of rumination; Cronbach's alpha for the current study was α = 0.95 indicating excellent reliability.

A Shortened Version of the Mood and Anxiety Scale Questionnaire (Watson et al., 1995): A 38- item inventory in which frequency of symptoms is indicated on a Likert scale ranging from 1 (*"not at all"*) to 5 (*"extremely"*), assessing subscales of 'Anxious Arousal' and 'Anhedonic Depression' (which further partitioned into 'Positive Affect' and 'Loss of Interest' subscales). Higher scores indicated higher levels of anxiety and/or depression; Cronbach's alpha for the current study was α = 0.91 indicating excellent reliability.

Hospital Anxiety and Depressions Scale (HADS; Zigmond and Snaith, 1983): The HADS is a 14-item inventory assessing anxiety and depression, in which frequency of symptoms are indicated on a Likert scale ranging from 0 (*"not at all"*) to 3 (*"most of the time"*). Higher scores indicated higher anxiety and/or depression; Cronbach's alpha for the current study was α = 0.81 indicating good reliability.

Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog, Version 3; (Wagner, Wagner et al., 2009): A 37-item inventory assessing perceived cognitive abilities and perceived cognitive impairments. Scores are indicated on a Likert scale ranging from 0 *("never")* to 4 ("*several times a day*"). Greater scores indicate better perceived cognitive functioning; Cronbach's alpha for the current study was α = 0.94 indicating excellent reliability.

The Fatigue Symptom Inventory (Hann et al., 1998): A 14 item inventory designed to assess the severity, frequency and interference of fatigue. Scores are indicated for 'severity' on an 11 point Likert scale ranging from 0 ("*not at all fatigued*") to 10 ("*as fatigued as I could be"*), 'frequency' on a 7 point Likert scale (0–7) indicating the number of days in the past week they felt fatigued, as well as an 11 point scale indicating the extent of each day on average they felt fatigued ranging from 0 (*"none of the day")* to 10 ("*the entire day*"), and 'perceived interference' on an 11-points scale ranging from 0 ("*no interference*") to 10 ("*extreme interference*") that assesses the degree to which fatigue in the past week was judged to interfere with general level of activity. Higher scores indicate greater levels of fatigue; Cronbach's alpha for the current study was α = 0.95 indicating excellent reliability.

Participants in the cancer survivors group additionally completed the following questionnaires which related specifically to their diagnosis: Quality of Life in Breast Cancer Patients Scale (Ferrell and Dow, 1997), which assesses the physical, psychological, social and spiritual dimensions of breast cancer patients. Scores are indicated on a Likert scale ranging from 0 ("*no problem*") to 10 ("*severe problem*"). Higher scores indicate better outcomes. Cronbach's alpha for the current study was α = 0.85 indicating excellent reliability. Cancer related thoughts was assessed by the Cancer Impact of Events Scale (IOE), (Weiss, 2007) whereby frequency of symptoms is indicated on a Likert scale ranging from 0 ("*not at all*") to 4 ("*extremely*"). Higher scores indicated worse outcomes. Cronbach's alpha for the current study was α = 0.88 indicating excellent reliability. Cancer Worry Scale (Custers et al., 2014) is an 8 item inventory which assesses worry associated with cancer recurrence. Scores are indicated on a Likert scale ranging from 1 ("*not at all or rarely*") to 4 ("*almost all the time*"). Higher scores indicate higher levels of worry. Cronbach's alpha for the current study was α = 0.82 indicating good reliability. Fear of Cancer Recurrence Scale (Simard and Savard, 2009) which is a 42 item inventory which assesses cancer recurrence fears. Responses are scored on a Likert scale ranging from 0 ("*never*") to 4 ("*all the time*"). Greater scores indicated higher levels of fear. Cronbach's alpha for the current study was α = 0.86 indicating excellent reliability.

2.3. EEG recording and data reduction

2.3.1. Flanker task

Continuous electroencephalographic (EEG) activity was recorded using the BrainVision system (Brain Products, Gilching, Germany), BrainAmp standard amplifier system, bandpass = 0.5–0.70 Hz. Recordings were taken from 32 Ag-AgCl electrodes, with 6 mm central opening, placed in accordance with the 10/20 system which comprised of both left and right mastoids. Electro-oculogram (EOG) activity generated by eye movements and blinks was recorded at FP1 and via additional electrodes placed inferior to the right pupil and on the left and right outer canthi which were all approximately 1 cm from the pupil. Electrode impedances were below 10 k Ω during testing. Electroencephalogram was initially referenced online to FCz and all electrical signals were digitized at 1024 Hz using the BrainVision recording software (Brain Products, Gilching, Germany).

Offline analyses were subsequently performed using BrainVision Analyzer 2 (Brain Products, Gilching, Germany). Scalp recorded electrodes were band pass filtered with cut-offs of 0.01 and 30 Hz (12 dB/oct roll off), and referenced to the numeric mean of the mastoids. Ocular artifacts were corrected using the procedure developed by Gratton et al. (1983). Response-locked data were segmented into individual epochs beginning at 200 ms prior to response onset and continuing for 800 ms post response. Then, physiological artifacts were identified using a computer-based algorithm build into BrainVision software. Trials failing to meet the following criteria were rejected: a voltage step exceeding 50 μV between contiguous sampling points, a voltage difference of more than 200 μV within a trial, or a maximum voltage difference less than 0.5 μV within a trial. This resulted in a loss of an average of 5.26% of trials across participants. Following this, the average activity was taken within the specified time windows for the ERN and Pe, and baseline corrected 200 ms before the response. Interpolation was completed by following the spherical splines method as reported in Perrin et al. (1989). Sixteen participants had electrodes interpolated, with no participant exceeding four interpolated electrodes. Of these participants, only one had electrodes interpolated that were included in their average for the ERN, CRN, and Pe values. No participants were excluded based on trial cut-offs for reliability analyses. For the BC Survivors group, the number of trials included in the final analysis ranged from 5 to 61 for error trials (M = 21, SD = 14), and ranged from 350 to 475 for correct trials (M = 438; SD = 27). For the Non-Cancer group the number of error

trials included in the analyses ranged from 3 to 66 (M = 21, SD = 16), while for correct trials the number of trials ranged from 339 to 474 (M = 430; SD = 27). Reliability was spearman corrected, and was as follows for the sample - (ERN – $r = 0.32$, $p = .01$; CRN – $r = 0.96$, $p < .001$; ERN Difference – $r = 0.45$, $p < .001$; Early Pe (Error) – $r = 0.55$, $p < .001$; Early Pe (Correct) – $r = 0.97$, $p < .001$; Early Pe (difference) – $r = 0.47$, $p < .001$; Late Pe (Error) – $r = 0.60$, $p < .001$; Late Pe (Correct) – $r = 0.95$, $p < .001$; Late Pe (Difference) – $r = 0.53$, $p < .001$).

2.3.2. Procedure

The experiment was conducted in a single lab based testing session in a sound proofed testing cubicle at Birkbeck, University of London, UK. Participants were tested individually, with each session taking approximately 2.5 h. Participants firstly gave informed consent, and then continued on to complete the battery of self-report questionnaires. The EEG cap and electrodes were then applied by the experimentor. The partcipants then completed the flanker task whilst their EEG activity was recorded. After completion of the flanker task the EEG cap was removed and participants were paid.

2.3.3. Statistical analyses

ERP and behavioural data were analysed using EPrime, IBM SPSS Statistics, Version 26.0 and BrainVision Analyzer 2 (Brain Products, Gilching, Germany). A series of independent samples *t*-tests and chi-square tests were used to compare demographic, self-reported cognitive and emotional vulnerability questionnaires and behavioural performance. Sensitivity power analysis for our sample of 62, with a desired power of 0.80, for an intended mixed ANOVA with interaction effects, revealed a minimum detectable effect size benchmark value of 0.04 (in partial eta-squared) corresponding to a Cohen's F of 0.21.

2.4. Behavioural analyses

2.4.1. Flanker task

Pre-processing of the flanker data ensured that blocks incorporating failed response mapping were discarded; if a participant reached the error threshold (≥60% errors) within a block, the appropriate segments were removed from the behavioural and ERP data. Overall congruency reaction time effects were analysed by a 2 (Congruency: Congruent vs. Incongruent) × 2 (Group: BC Survivors vs Non-Cancer) mixed ANOVA. Similarly, accuracy effects were analysed by a 2 (Accuracy: Accurate vs. Inaccurate) × 2 (Group: BC Survivors vs Non-Cancer) mixed ANOVA.

2.5. EEG analyses

2.5.1. ERN

The ERN and the CRN were defined on error and correct trials, respectively as the average voltage occurring in the 0-100 ms post response time window at Cz where the ERN and CRN were maximal. To establish whether the expected ERN effect was present and to observe any group differences a 2 (Accuracy: Error vs. Correct) × 2 (Group: BC Survivors vs Non-Cancer) mixed ANOVA was conducted. A difference wave approach was also used to isolate error-related neural activity by subtracting the ERP waveform on correct trials from incorrect trials. Group comparisons of voltage difference scores were analysed with independent *t*-tests.

2.5.2. Pe

The Pe and its correct trail counterpart were quantified as the average voltage in the 150- to 350-ms (Early Pe) and 350- to 550-ms (Late Pe) post-response time window consistent with prior work (Schroder et al., 2014). Recent research indicates that the Pe consists of two subcomponents, with an early Pe reflecting a continuation of the ERN and a late Pe reflecting error awareness (Van der Borght et al., 2016). The Pe was quantified at Pz where it was maximal. The Pe was analysed with a 2 (Accuracy: Error vs. Correct) × 2 (Group: Breast Cancer Survivors vs Non-Cancer) mixed ANOVA.

3. Results

3.1. Demographic measures

Table 1 indicates group characteristics on demographic variables for the sample of 62. Group differences were found for marital status, X^2 (5) = 21.31, $p = .001$, such that more women in the breast cancer survivors' group were married. No other group differences were found for any other demographic variable, (all *p*'s > 0.07).

3.2. Self-reported cognitive and emotional functioning

Mean self-reported symptomatology for each group is presented in Table 2. Analyses indicated that perceived cognitive functioning was better for the non-cancer compared to breast cancer survivors, t (60) = 6.23, $p < .001$, $d = 1.23$. There were no group differences for measures of anxiety, rumination, depression or fatigue (all *t*'s < 0.39, all *p*'s > 0.31).

3.3. Behavioural performance

Behavioural performance data are displayed in Table 3. Analyses showed a main effect of congruency indicating that RTs were faster on congruent trials compared to incongruent trials, $F(1, 60) = 497.74$, $p < .001$, $\eta_p^2 = 0.89$. Breast Cancer Survivors showed somewhat faster responses overall than the Non-Cancer Group, (Breast Cancer survivors, Congruent: M = 505.79, SD = 44.85, Incongruent: M = 547.77, SD = 45.57; Non-Cancer, Congruent: M = 528.81, SD = 56.81, Incongruent: M = 569.91, SD = 49.59), although the main effect of group did not reach significance, $F(1, 60) = 3.28$, $p = .07$, $\eta_p^2 = 0.05$, nor did the interaction between Group and Congruency, $F < 1$. Total accuracy analyses showed a main effect of accuracy such that there were more correct responses than errors, $F(1, 60) = 4557.77$, $p < .001$, $\eta_p^2 = 0.98$. However no differences were found for the main effect of Group, $F(1, 60) = 2.96$, $p = .09$, $\eta_p^2 = 0.05$, and no interaction effect was found between Group and Accuracy, $F(1, 60) = 2.03$, $p = .16$, $\eta_p^2 = 0.03$. Thus,

Table 2
Mean self-report symptomatology total scores for each group (breast cancer and non-breast cancer).

	Breast cancer (*n* = 30)		Non-cancer (*n* = 32)		*P*
Rumination Response Scale	42.67	(13.96)	42.63	(14.94)	.99
Mood and Anxiety Scale Questionnaire					
Anhedonic Depression	56.57	(13.35)	54.47	(18.77)	.61
Anxious Arousal	26.87	(6.55)	25.16	(7.18)	.33
Hospital Anxiety and Depressions Scale	19.1	(7.02)	17.19	(7.88)	.32
Functional Assessment of Cancer Therapy Cognitive Scale	75.96	(21.79)	101.46	(19.56)	<.001*
Fatigue Symptom Inventory	54.37	(22.01)	57.16	(31.12)	.69
Quality of Life in Breast Cancer Patients Scale	222.83	(49.81)	_	_	_
Cancer Impact of Events Scale	20.7	(12.47)	_	_	_
Cancer Worry Scale	16.57	(3.95)	_	_	_
Fear of Cancer Recurrence	78.33	(21.41)	_	_	_

Note. Standard deviations are in parentheses.
* Significant between-group difference, $P = .05$.

Table 3
Means and standard deviations for behavioural performance and ERP's elicited from the flanker task.

	Breast cancer (*n* = 30)		Non-cancer (*n* = 32)		*t*	*P*
Flanker task						
No. errors	19.53	(14.25)	20.89	(16.51)	0.35	.73
Accuracy (%)	95.78	(3.05)	95.33	(3.79)	0.52	.61
Error RT (ms)	460.81	(88.77)	478.81	(92.5)	0.78	.44
Correct RT (ms)	529.92	(43.48)	550.88	(52.27)	1.71	.09
Congruent RT (ms)	505.81	(44.85)	528.81	(56.81)	1.76	.08
Incongruent RT (ms)	547.57	(45.57)	569.91	(49.61)	1.83	.07
ERPs						
Error-related negativity (ERN)	−1.95	(2.84)	−2.10	(2.30)	0.24	.81
Correct-response negativity (CRN)	1.28	(2.07)	−0.28	(1.75)	3.23	.002*
ΔERN	−3.23	(3.21)	−1.81	(2.18)	2.05	.04*
Early Pe Errors	2.04	(2.78)	1.08	(4.81)	0.95	.35
Early Pe Corrects	−2.67	(3.05)	−3.55	(2.65)	1.20	.23
Late Pe Errors	3.20	(4.81)	0.85	(4.43)	2.01	.04*
Late Pe Corrects	−2.91	(2.25)	−3.97	(2.71)	1.64	.11
ΔPe Early	4.71	(3.43)	4.63	(4.81)	0.08	.93
ΔPe Late	6.11	(5.14)	4.81	(4.44)	1.06	.29

Note. Standard deviations are in parentheses.
ERN and CRN means reflect average at sites Cz. Pe means reflect average at sites Pz. Mean early and late Pe scores were used to create the Pe difference score.
* Significant between-group difference, $P = .05$.

overt cognitive performance did not significantly differ between groups.[1]

3.4. ERPs

3.4.1. ERN/CRN

Means, standard deviations and independent samples *t*-tests are presented in Table 3. Fig. 1 presents response-locked waveforms and scalp distribution maps for the ERN. At the time of response, errors elicited a larger negativity (i.e. the ERN) than correct responses, confirmed by a significant main effect of response type, $F(1, 60) = 52.78$, $p < .001$, $\eta_p^2 = 0.47$, showing the typical ERN waveform. The main effect of group missed significance, (Breast Cancer Survivors, Errors: M = −1.95, SD = 2.84, Corrects: M = 1.28, SD = 2.07; Non-Cancer, Errors: M = −2.10, SD = 2.30, Corrects: M = −0.28, SD = 1.75), $F(1, 60) = 3.51$, $p = .06$, $\eta_p^2 = 0.05$. Consistent with predictions, there was a significant interaction between response type and group, $F(1, 60) = 4.21$, $p = .04$, $\eta_p^2 = 0.07$. As indicated in Fig. 2, follow up analyses showed that this interaction was driven by a significant CRN amplitude difference between groups such that the CRN was smaller for the Breast Cancer Survivor group compared to the Non-Cancer control, $t(60) = 3.23$, $p = .002$, $d = 0.81$. This between group difference was not however found for the ERN, $t < 1$. Correspondingly, the voltage difference between the ERN and CRN (i.e., ΔERN) was larger in the Breast Cancer Survivor, compared to the Non-Cancer control group, $t(60) = 2.05$, $p = .04$, $d = 0.52$.

3.4.2. Pe

Fig. 3 presents response-locked waveforms and scalp distribution maps for the Pe. In the 150- to 350-ms post-response time window, the main effect of response type indicated that error trials were associated with greater positivity compared to correct trials, $F(1, 60) = 76.49$, $p < .001$, $\eta_p^2 = 0.56$, confirming the presence of an early Pe. The main effect of Group was non-significant, $F(1, 60) = 1.72$, $p = .19$, $\eta_p^2 = 0.02$, as was the Accuracy × Group interaction, $F < 1$.

In the 350- to 550-ms post-response time window, the main effect of response type was again significant, $F(1, 60) = 84.43$, $p < .001$, $\eta_p^2 = 0.57$, showing a late Pe. Importantly, the main effect of Group was also significant, $F(1, 60) = 5.55$, $p = .02$, $\eta_p^2 = 0.09$, indicating that Breast Cancer Survivors had a significantly larger late Pe compared to the Non-Cancer control group. The Accuracy × Group interaction was non-significant, $F(1, 60) = 1.14$, $p = .29$, $\eta_p^2 = 0.02$ (see Fig. 4).

4. Discussion

The primary aim of this study was to investigate neurocognitive efficiency by measuring the neurocognitive correlates of error processing in breast cancer survivors. Whilst numerous fMRI studies have been conducted in the area of CRCI in breast cancer survivors (see Ahles and Root, 2018, for a review) investigation into ERP components is lacking, and no previous study has considered the ERN and the Pe in the breast cancer population. During a flanker task designed to challenge cognitive-control related performance monitoring, we measured the neural activity of both a group of breast cancer survivors and a group of non-cancer control participants. We additionally used a series of emotional and cognitive self-report measures to account for previously documented differences between groups in these domains.

Findings firstly indicate that for both groups the typical ERN and Pe waveforms were present establishing that this pattern is present in the breast cancer survivor as well as the non-cancer population. For the ERN, results show that there was a greater ΔERN in breast cancer survivors, illustrating differential early performance monitoring. The ΔERN measure has been widely used as an index of performance monitoring in individual differences studies, as it helps isolate error-specific neural activity or the relative difference in neural activity on errors versus corrects (Klawohn et al., 2020; Luck, 2014). Unexpectedly, the ΔERN appears to be driven by a smaller CRN amplitude for the breast cancer survivor group compared to non-cancer controls; that is, the typically negative CRN appears to be blunted in women affected by breast cancer. Due to the CRN's comparable morphology and source with the ERN, it has been suggested that they can reflect the same cognitive control process during response monitoring (Meckler et al., 2011). This has been supported by independent component analyses (Roger et al., 2010; Hoffmann and Falkenstein, 2010) and studies that show the value of the CRN in predicting the quality of a subsequent response. For instance, a smaller CRN on a given trial can predict the occurrence of an error in the subsequent trial (Allain et al., 2004). Thus, like the ERN, the CRN reflects an important aspect of performance monitoring, such that when monitoring is low, the next trial is more likely to be erroneous. That said, the CRN might reflect somewhat difference processes from the ERN, albeit still related to performance monitoring (Endrass et al., 2012; Olvet and Hajcak, 2008; Yordanova et al., 2004).

Importantly, the current findings suggest that for the breast cancer survivor group, there is a decreased ability to monitor performance and evaluate the need for implementing cognitive control processes at early stages of processing. This mirrors performance monitoring findings with other clinical populations who show cognitive control related deficits. For example, both a decreased ERN and CRN have been observed in patients diagnosed with Schizophrenia, indicating abnormal performance monitoring (Bates et al., 2002; Martin et al., 2018; Foti et al., 2020). It must be noted, however, that the current interpretation must be taken with caution. Although breast cancer survivors had a decreased CRN, there were no differences between groups in overall behavioural performance. This discrepancy between brain and behaviour does not suggest however that breast cancer survivors would not experience cognitive dysfunction in the real world. Indeed, our results indicate that the breast cancer survivor group reported significantly greater perceived cognitive impairments compared to the non-cancer group, suggesting that the neural changes observed may translate to their perception of cognitive functioning. In fact, these findings have important

[1] Further data collected as part of a larger investigation showed that the were no group differences on working memory performance as measured by the OSPAN task, $t(60) = 1.27$, $p = .21$, $d = 0.42$, (see Supplementary material).

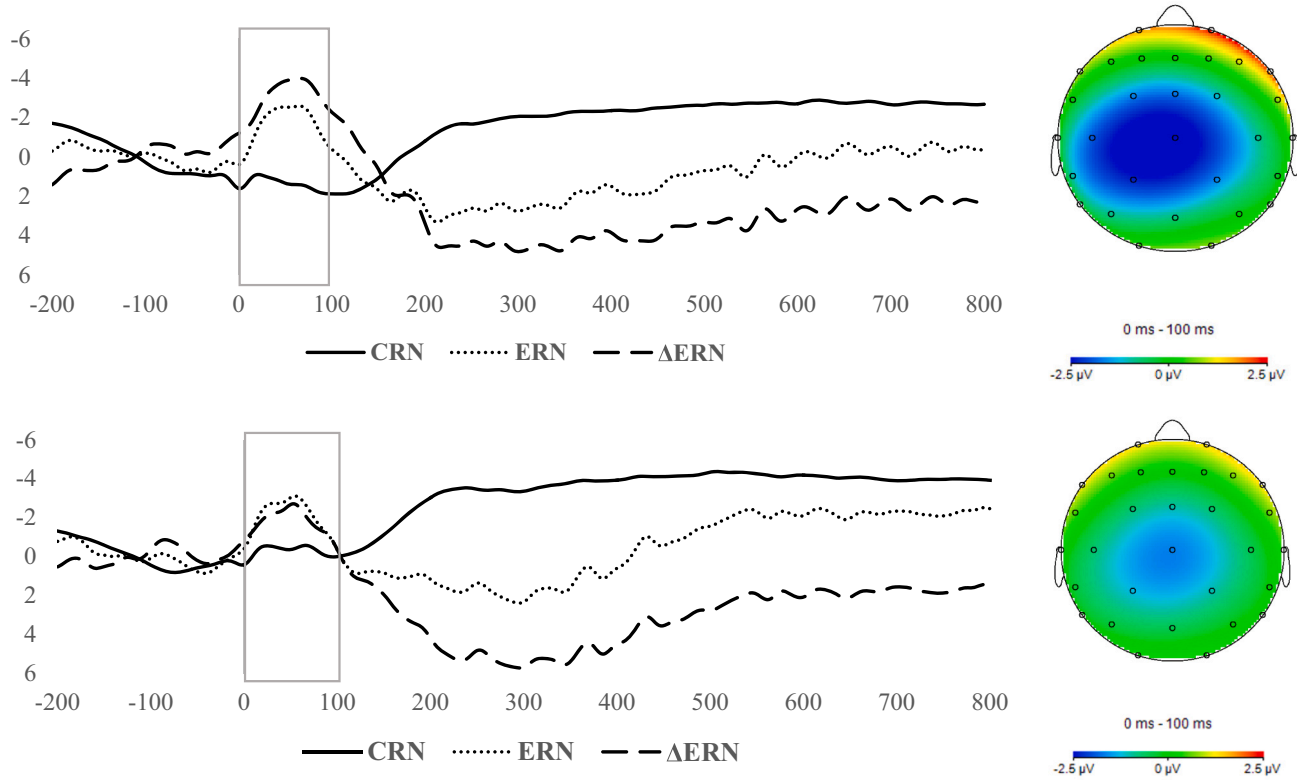

Fig. 1. Response-locked ERP waveforms recorded from the flanker task at Cz for the breast cancer group (top) and non-cancer (bottom) group. On the right are scalp topographies representing the error-related negativity (ERN) derived from the average waveform for error trials.

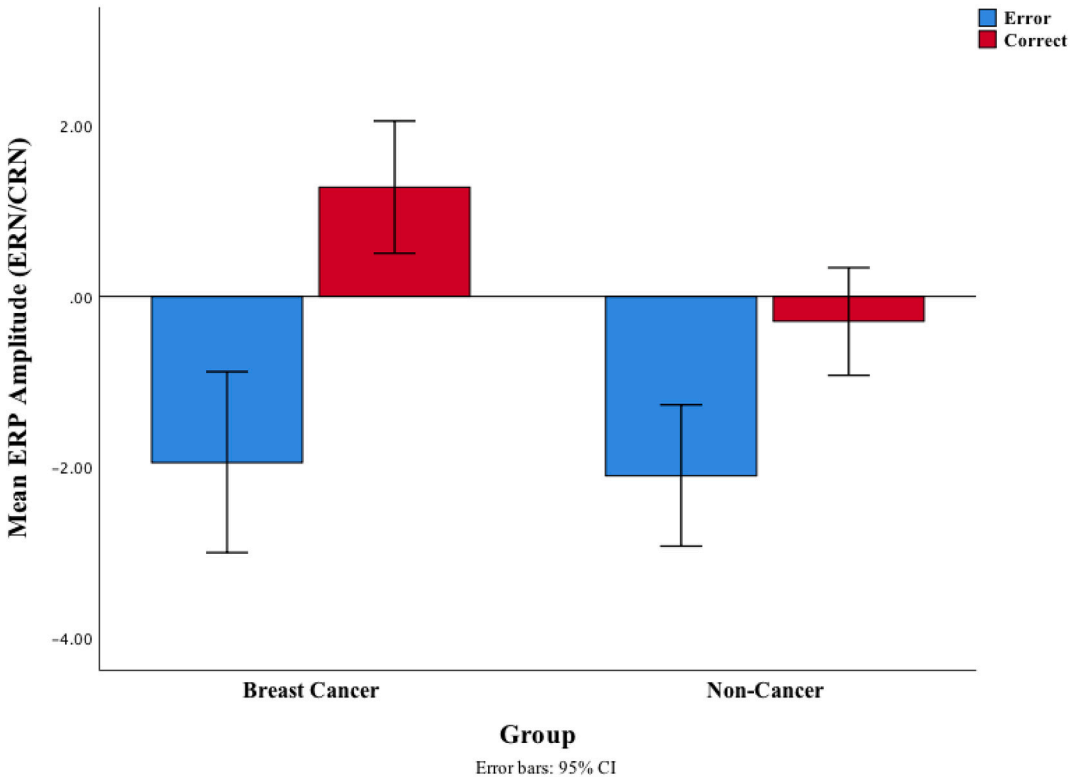

Fig. 2. Response-locked Mean ERN and CRN amplitude for each group (Breast Cancer and Non-Cancer).

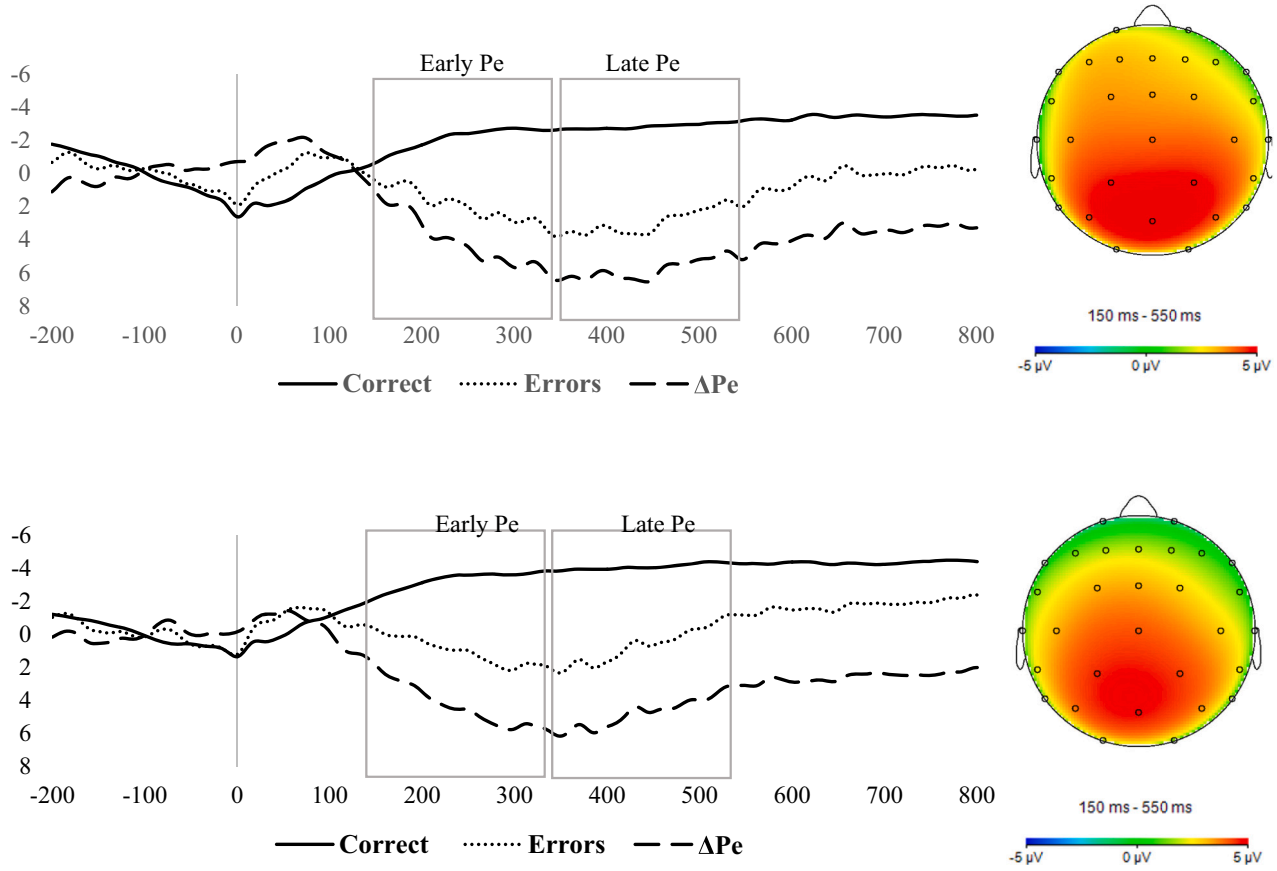

Fig. 3. Response-locked ERP waveforms recorded from the flanker task at Pz for the breast cancer group (top) and non-cancer (bottom) group. On the right are scalp topographies representing the error positivity.

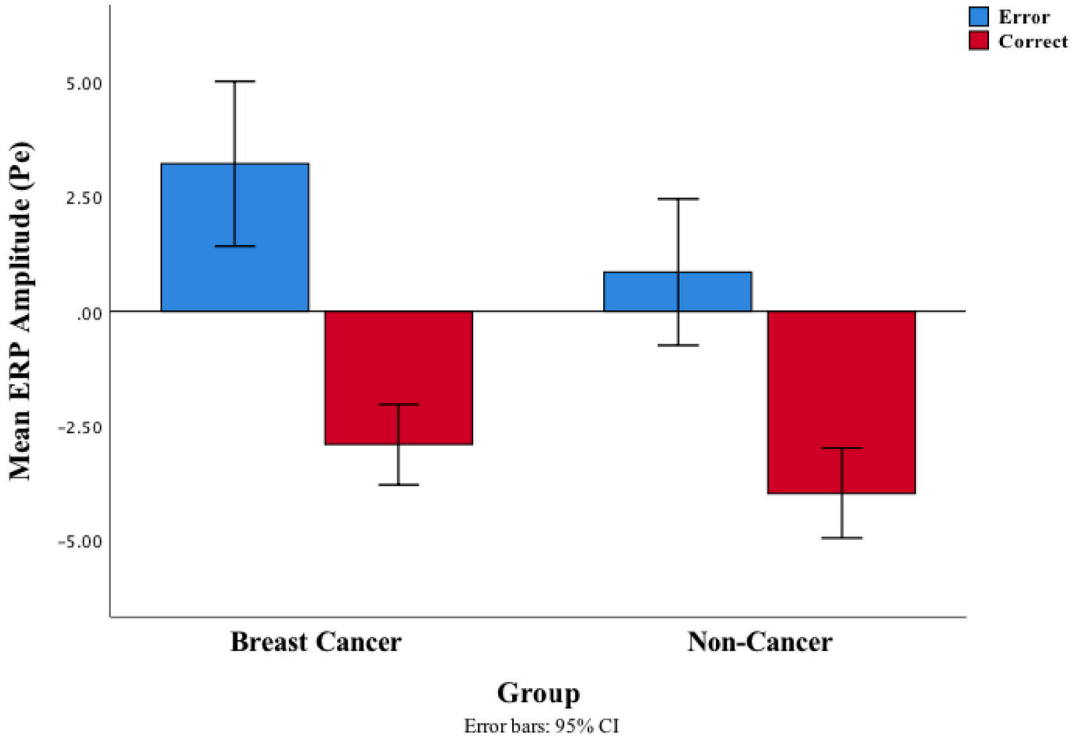

Fig. 4. Response-locked Mean Pe amplitude for correct and error response type for each group (Breast Cancer and Non-Cancer).

implications for one of the major conundrums in the field of CRCI – the mismatch between objective and subjective reports often observed in cancer populations (Hutchinson et al., 2012; Costa and Fardell, 2019). It further emphasises the problematic nature of solely measuring cognitive function through behavioural measures in which tests are administered in an environment designed to minimise distraction and maximise performance (Ahles and Hurria, 2018). Whilst performance may be comparable to a non-cancer population under controlled conditions in a lab-based environment, behavioural deficits may manifest over time under the pressures of daily life, through the greater fatigue that may result from more effortful and lower neurocognitive efficiency.

Interestingly, following a blunted CRN and greater ΔERN, the current findings indicate that the breast cancer survivor group had a significantly larger late Pe compared to the non-cancer group in the absence of performance effects on the flanker task. We suggest the observed difference to be indicative of neural compensatory mechanisms through the conscious processing of performance monitoring, corroborating previous neuroscientific findings in women affected by breast cancer (McDonald et al., 2012; Menning et al., 2015; Menning et al., 2018). Considering that the Pe may represent the conscious awareness of an error and the allocation of attentional resources necessary for behavioural adjustments and improved performance (Steinhauser and Yeung, 2010; Gehring et al., 2012), these findings have important implications for breast cancer survivors. Via compensatory mechanisms, greater neural activation was necessary to allocate attention to the task in order to maintain behavioural performance. This finding comports with related work showing that cancer survivors frequently report that they are more susceptible to distraction during cognitive tasks that require greater effort (Von Ah et al., 2013). It further emphasises the noted disparity between objective and subjective reports so often observed in cancer populations.

The idea of neural compensatory mechanisms at play in CRCI has been highlighted in recent reviews (Reuter-Lorenz and Cimprich, 2013; Andryszak et al., 2017; Ahles and Root, 2018; Horowitz et al., 2018; Lange et al., 2019), with patterns of hypoactivation and hyperactivation taken as signs of neurocognitive inefficiency. Whilst hypoactivation can be interpreted as a failure to recruit relevant neural regions to perform a task, hyperactivation can indicate the need for exaggerated recruitment to maintain task performance. Whilst these compensatory mechanisms are usually observed in the prefrontal cortex supporting deficits in working memory (McDonald et al., 2012; Menning et al., 2015; Menning et al., 2018), they can extend to higher task-related hippocampal-cortical connectivity related to self-reported cognitive concern (Apple et al., 2018) and greater activation in parietal regions during visuo-spatial tasks (Menning et al., 2017). Indeed, cognitive effort (the amount of attention allocation to perform a given task) as indexed by pupillary response has been shown to be greater for breast cancer survivors compared to non-cancer controls, in the absence of performance effects, on standard neuropsychological tests. Greater pupillary dilation was further correlated with worse self-report measures of cognitive functioning (Myers et al., 2019)

Relatedly, compensatory error monitoring hypotheses have been recently developed for other populations who, like cancer patients, typically show cognitive-control related deficits (i.e. anxiety, schizophrenia), (Moser et al., 2013; Moser, 2017; Chen et al., 2017). Whilst our results suggest that prefrontal cognitive alterations likely result from the effects of cancer diagnosis and treatment itself, rather than high levels of anxiety or emotional distraction per se, we would suggest that a similar compensatory mechanism may account for our findings. That is, a greater ΔERN and enlarged Pe in breast cancer survivors is a sign of neurocognitive inefficiency in performance monitoring that requires a greater conscious allocation of resources to reach an adequate level of performance. It appears that under controlled settings, as a result of compensatory neuroplasticity, breast cancer survivors can maintain a comparable level of cognitive performance to non-cancer controls. That said, like the current study, previous fMRI research has indicated that additional brain regions are involved in the performance of low difficulty tasks, allowing performance to remain within pre-cancer norms. Greater decline in function can become apparent with increasing task difficultly, when task-demands exceed the efficiency of compensatory mechanisms (Reuter-Lorenz and Cimprich, 2013; Andryszak et al., 2017). This is an important line for future investigation in breast cancer survivorship.

Taken together, the current findings corroborate and build upon this growing picture of altered neural activation to support various cognitive functions, indicating that cognitive-control related performance monitoring is also altered in breast cancer survivorship as indexed by a blunted CRN, a greater ΔERN and a larger Pe. This is interesting because it suggests that the earliest stage of performance monitoring, which is considered an automatic process, without volition, is blunted for women affected by breast cancer. Following this, when performance processing becomes under greater conscious control, the current findings show the need for greater neural recruitment and more effortful processing.

When considering neural compensatory mechanisms, it is of further importance to consider other factors that could have contributed to hyperactivation of certain brain regions. As discussed, no group differences were found for levels of anxious and depressive symptomatology and therefore findings cannot be attributed to abnormal error processing as a result of emotional disorder as previous ERN studies have found (Olvet and Hajcak, 2008).

Similarly, across the CRCI literature, whilst studies have suggested that biological and psychosocial variables such as fatigue, worry and stress are related to cognitive dysfunction in cancer, none of the proposed factors have consistently and reliably predicted or explained CRCI (Menning et al., 2017), a pattern that is emphasized by our findings. Given the plethora of evidence pointing to CRCI stemming from the neurotoxic effects of cancer treatment (Moore, 2014), the growing evidence that points to the direct effects of cancer itself (Ahles and Root, 2018), and the numerous studies that point to cognitive compensatory mechanisms in breast cancer survivors, it seems unlikely that the current findings could be primarily attributed to other variables. Indeed, all our participants in the breast cancer survivor group had undergone chemotherapy, and we found no influential effects of numerous potential confounding variables that were assessed.

A key aim moving forward will be to illuminate the time course of neural change across the cancer trajectory. Both hyperactivation and hypoactivation of certain brain regions supporting cognitive functions have been observed at different stages along the cancer continuum (see Andryszak et al., 2017 for a review). For instance, longitudinal studies have shown task-related prefrontal hyperactivation at baseline, a drop in activation one-month post chemotherapy, and a reappearance of prefrontal hyperactivation one year after chemotherapy (McDonald et al., 2012). Moreover, findings suggest that the over-recruitment of brain regions may depend both on the level of treatment toxicity that individuals are exposed to and the particular probed cognitive domain in response to decreased neural integrity (Menning et al., 2017).

A further complex challenge in the investigation of CRCI relates to the theory that cognitive deficits are determined by a complex interaction of cancer treatment, innate (e.g. genetic) and accumulated risk factors, and aging, making the elucidation of the exact mechanisms at play difficult. Ahles & Root (2018) advocate utilising the concept of tipping points in complex systems, in which early warning signs are detected before abrupt changes occur from one state to another. Similarly, Horowitz et al. (2018) suggest that a core priority should be to develop models of how hypothesized causal pathways for CRCI would propogate to the level of brain systems and cognitive functioning. A further recommendation is to develop new measures of cognitive function, specific to the impairments faced by cancer patients, in order to properly assess the subtle changes that may occur as a result of CRCI. Task paradigms and tools developed in cognitive neuroscience have the potential to measure discrete cognitive processes and discriminate which subcompenent processes underscore cognitive complaints. In line

with this goal, the current findings suggest that investigation of ERP's may serve as a cost-effective, non-invasive tool for early assessment of subtle neural changes that may prospectively predict overt decifits. A collaborative approach with the cooperation of neuroscientists and clinical researchers would facilitate this aim. Correspondingly, once a comprehensive picture of CRCI had been established, targeted cognitive rehabilitation programs should be developed in order to improve quality of life for survivors. Through more efficient cognitive funtioning, there is further potential to improve emotional regulation in breast cancer survivorship (Von Ah et al., 2012; Swainston and Derakshan, 2018).

4.1. Limitations

The current study has a number of limitations. Firstly, participants were recruited via social media platforms and therefore may not be representative of the wider popultaion of breast cancer survivors. Secondly, we did not include a comparison group of breast cancer survivors who did not undergo chemotherapy, and therefore we are unable to conclude whether the neural differences observed are a result of the neurotoxic effects of chemotherapy or other potential contributing factors in the development of cognitive dysfunction such as the biology of the disease itself or other treatment modalities (e.g. hormone therapy), which many of the participants were taking. Evidence shows that tamoxifen, for example, may also play a role in cognitive inefficiency in breast cancer survivorship (Castellon et al., 2004). Similarly, we did not assess for different doses and varying types of chemotherapy treatment, which may also influence cognitive functioning in cancer populations. Thirdly, the ERP measures in the current study demonstrated fairly low internal consistency across both groups. Insofar as these low estimates might reflect lower data quality, future investigations will surely be needed to replicate the current findings (Clayson et al., 2021). Lastly, we do not have pre-treatment baseline measures of neural activity and cognitive performance, or immediately after treatment and thus we are unable to conclude whether any neural changes in patterns of activation are a continued deterioration, or representative of partial recovery after active treatment.

5. Conclusions

The current study was the first of its kind to investigate cognitive-control related performance monitoring in the breast cancer population. Compared to non-cancer controls, the findings point to an altered pattern of neural recruitment throughout the performance monotoring process for women affected by breast cancer. Specifically results indicated an early, blunted neural activation for correct trial reponse, followed by an increased neural activation throughout the conscious awareness of performance. These findings have important implications for developing cognitve rehabilitation programmes for breast cancer survivors affected by cognitive decline and illuminate performance processing as a novel treatment target.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2021.06.013.

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