Supportive Care in Cancer (2019) 27:1121–1128
https://doi.org/10.1007/s00520-018-4401-0

ORIGINAL ARTICLE

Pupillary response: cognitive effort for breast cancer survivors

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Received: 11 May 2018 / Accepted: 3 August 2018 / Published online: 10 August 2018

Abstract

Purpose The *purpose* of this cross-sectional comparative pilot study was to evaluate cognitive effort, indexed by pupillary response (PR), for breast cancer survivors (BCS) with complaints of cognitive dysfunction following chemotherapy.

Study Aims Compare the cognitive effort employed by BCS to healthy controls (HC) during neuropsychological tests (NPT) for memory, sustained attention, verbal fluency, visuospatial ability, processing speed and executive function; and Investigate the relationship between PR-indexed cognitive effort and participants' self-report of cognitive function.

Methods Self-report of cognitive function was collected from 23 BCS and 23 HC. PR was measured during NPT. Independent two-sample *t* tests or Wilcoxon rank sum tests were used to compare group scores. Between-group effect size (Cohen's *d*) was calculated for each outcome. Correlation between mean self-report scores and PR values, as well as 95% confidence intervals, was calculated.

Results No group differences were demonstrated for NPT performance. BCS reported more issues with cognitive function than HC ($p < .0001$). A group effect for BCS was seen with PR-indexed cognitive effort for components of most NPT ($p < .05$). PR was correlated with most self-report measures of cognitive function ($r = 0.33–0.45$).

Conclusions PR sensitivity to cognitive effort across a variety of NPT and correlation with self-report of cognitive function was demonstrated. The portability, affordability, and "real-time" aspects of PR are attractive for potential use in the clinic setting to assess cognitive function. A larger study is needed to confirm these results. Prospective investigation of PR in BCS is needed to demonstrate sensitivity to cognitive function changes over time.

Keywords Breast cancer · Cognitive dysfunction · Cognitive neuroscience · Pupillary response

Introduction

Cancer- and cancer treatment-related cognitive dysfunction is commonly experienced by cancer survivors and has a significant impact on survivors' quality of life [1]. Proposed mechanisms for the cognitive dysfunction include direct injury to neural progenitor cells and accelerated aging resulting from impaired DNA repair mechanisms, inflammation, and oxidative stress [1]. Survivors complain of struggling with short-term memory, word finding, concentration, multi-

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tasking, or performing complex tasks [2]. These cognitive complaints can impact survivors' professional and social functioning [2–5]. The cognitive domains most commonly affected include memory, attention, verbal fluency, visuospatial ability, processing speed, and executive function [6–10]. Estimates of the prevalence of cognitive dysfunction during and shortly following cancer therapy for non-central nervous system (CNS) malignancies range as high as 78% [11]. Long-term dysfunction can last as long as 20 years following treatment [12]. Lack of correlation between standard neuropsychological tests (NPT) and cancer survivors' self-report of cognitive dysfunction has been attributed to lack of sensitivity of available NPT, the subtlety of cognitive changes experienced by survivors of non-CNS malignancies, and the possibility that objective and subjective tests may measure different constructs of cognitive function [13]. This disparity is further complicated by survivors' ability to compensate based on education level and cognitive reserve [14, 15]. Furthermore, the results of neuropsychological (NP) testing only reflect survivors' performance on cognitive tasks (frequently within normal limits), but do not reflect the cognitive effort needed to execute the task in real time. Much of the research to date has been conducted with breast cancer survivors (BCS) due to long survival time and a heightened awareness of the phenomenon within this population.

The concept of cognitive workload (the mental/cognitive effort or amount of attention allocated to perform a task) [16] may be key to the accurate assessment of cognitive function in cancer survivors. Neuroimaging currently is used in the context of investigation to assess changes in brain structure, neural activation, and functional connectivity. Functional neuroimaging studies involving cognitive tasks have demonstrated increased cognitive effort employed by BCS to achieve outcomes that are similar to those of healthy controls (HC) [17, 18]. However, neuroimaging is time consuming, costly, and may be burdensome for patients. Less expensive, but highly sensitive, assessment strategies are needed to further evaluate cognitive effort among survivors in order to better understand (i) the specific components of cognition affected by cancer and cancer therapy, (ii) predict the duration and severity of cognitive dysfunction, and (iii) assess the efficacy of interventions designed to improve cognitive function in this population.

Task-evoked pupillary response (PR) is an involuntary, autonomic reflex known to be a neurophysiologic marker of cognitive effort expenditure and allocation of cognitive resources [19–21]. Pupil dilation is controlled by the sympathetic and parasympathetic nervous systems. Performance of difficult and sustained cognitive tasks results in pupil dilation due to parasympathetic inhibition of the iris sphincter muscle. This inhibition is modulated through the Edinger-Westphal complex and results from increased activation of the locus coeruleus and secretion of norepinephrine [20, 22]. Remote tracking of PR has been used to demonstrate a linear relationship between the magnitude of pupil dilation and cognitive effort (workload) during NP testing and yields raw data for changes in pupillary diameter during cognitive tasks involving a stimulus and response [19, 21]. Advances in technology have led to the use of more portable eye trackers, as well as the development of eye tracking software that converts the raw pupil data into the Index of Cognitive Activity (ICA). This conversion involves the application of wavelet decomposition to estimate the average number of abrupt discontinuities in pupil size per second. Signal processing algorithms of wavelet analysis yield the ICA (a scaled measure of cognitive effort between 0 and 1). One advantage of ICA is differentiation of the pupillary response (PR) to cognitive challenges from accommodation to light [21]. Additionally, the signal smoothing eliminates statistical noise and hardware anomalies while accounting for rapid pupillary constrictions and/or slow dilations related to light exposure [21]. This process allows moment-to-moment assessment of pupillary changes and is not limited purely to changes resulting from response to a stimulus.

PR is not subject to the practice effects associated with repeated NP testing and may be a more accurate measure of cognitive effort [21]. Additionally, PR measurement is not invasive and provides an index of cognitive effort in real time. Pupillary response has been used widely in the field of psychophysiology and has been studied with populations of older adults [19, 23]. Our group recently demonstrated that measurement of PR discerns between patients at risk of cognitive decline due to Parkinson's disease and age-matched controls, in spite of similar behavioral performance on NPT [24, 25]. Similar results have been demonstrated with patients at risk for Alzheimer's disease [26]. These results corroborate the hypothesis that cognitive effort, indexed by PR, is more sensitive in detecting subtle cognitive changes than behavioral performance on NPT. However, the assessment of PR in BCS has not been studied and is of interest as an innovative, non-invasive, and potentially more sensitive measure of cognitive function compared with behavioral performance in NP testing. Translation of evidence from this successful cognitive neuroscience paradigm for neurologic disorders to the clinical setting for the BCS population may serve to enhance the sensitivity for assessment of cognitive function.

The *purpose* of this cross-sectional comparative pilot study was to evaluate cognitive effort, indexed by PR, for BCS with complaints of cognitive dysfunction following chemotherapy. The study *aims* were to (1) Compare the cognitive effort employed by BCS to HC during NPT for memory, sustained attention, verbal fluency, visuospatial ability, processing speed, and executive function; and (2) investigate the

relationship between PR-indexed cognitive effort and participants' self-report of cognitive function. We hypothesized that BCS would demonstrate greater cognitive effort than HC while achieving similar outcomes on the NPT. We expected a positive correlation between PR-indexed cognitive effort and participants' self-report of cognitive function.

Methods

Participants and settings

The University of Kansas Medical Center Human Subjects Committee approved the study. Participants were recruited from the University of Kansas Cancer Center and two Midwest Cancer Alliance sites: North Kansas City Hospital and Olathe Medical Center. Eligible women included those aged 40–65, diagnosed with stage I–III breast cancer, within 3 months to 6 years of having completed chemotherapy (and radiation if received), currently receiving endocrine therapy, and with complaints of cognitive dysfunction. On-going anti-HER-2 therapy was allowed. HC within the same age range and education levels also were recruited. Women were excluded if they, or the referring health-care provider, reported a history of severe clinical depression, Alzheimer's disease, dementia, or other conditions that would significantly affect cognitive function.

Instruments

Demographics

The study questionnaire included items related to ethnicity, marital and work status, and years of education. The Women's Health Initiative Brief Physical Activity Questionnaire (WHI PAQ) was used to collect data on participants' activity levels and to calculate total MET (metabolic equivalent of task) hours per week, as exercise has been shown to potentially reduce inflammation and self-report of decreased cognitive function [27, 28].

Perceived cognitive function

Participants' self-report of cognitive function was measured with instruments developed for, and/or validated with, the cancer survivor population. Data were collected with the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog, version 3) subscales for Perceived Cognitive Impairment (PCI), Perceived Cognitive Abilities (PCA), and Quality of Life (QOL) [29]. Higher subscale scores indicate better perceived cognitive function and QOL. Data also were collected with two of the Patient Reported Outcomes Measurement Information System (PROMIS) Applied Cognition 8-item short forms for General Concerns and Abilities [30]. T-scores for both short forms are used in the analyses. Higher scores for General Concerns indicate worse cognitive function. Higher scores for Abilities indicate better perceived cognitive function.

Objective cognitive function

Psychometrically sound NPT were selected to objectively measure function across a variety of cognitive domains [31, 32]. The Wechsler Adult Intelligence Scale (WAIS, 4th edition) Letter Number Sequencing (LNS) test measured auditory, short-term working memory. Participants must verbally recall a sequential series of letters and numbers (increasing in difficulty from two to eight characters) giving the numbers first (ascending order) followed by the letters (alphabetical order). Outcomes include scaled scores for the number of correct sequences and a score for the longest correct sequence.

The Wechsler Memory Scale (WMS, 4th edition) Logical Memory (LM) I and 2 were used to measure auditory short-term and delayed working memory. Participants listen to and verbally repeat two short stories as close to verbatim as possible. After a delay, participants repeat the stories without prompting and then must respond to specific yes/no questions about the story content. Outcomes include scaled scores for the number of correct idea units and responses.

The F-A-S test measures verbal fluency and retrieval. Participants are given 60 s each to say as many words as they can that begin with the letters F, A, and S. A score is calculated for the total number of words the participants provide.

The N-back test is a measure of working memory and sustained attention. A series of individual letters is presented at a constant pace (5 s apart). For each of the three components of the test, participants are asked to indicate when they see a letter that is "n"-back from the target letter. Each task lasted 5 min (with a brief rest period between episodes) and included 5 target letters and 15 distractors. We conducted 0-, 1-, and 2-back tests.

Tests for visuospatial ability (Rey-Osterrieth Complex Figure Test) processing speed (Trail Making A & B) and the task switching component of executive function (Trail Making B) were not included a priori due to interference with capture of the PR [32].

Study procedures

Following informed consent, participants completed the study questionnaire. Participants were seated 60–80 cm away from the FX3 eye tracker (SeeingMachines, Inc., Canberra, Australia) placed beneath a 9.7-in. iPad Air 2 (A1566, Apple Inc., 2014). The iPad was mounted at eye height on a height-adjustable table. EyeWorks™ software (EyeTracking, Inc., California) was used to calibrate the eye tracker to each

Table 1 Comparison of demographics

Variable[a]	Specifics	BCS Frequency (%)	HC Frequency (%)
Ethnicity			
	Not Hispanic or Latino	23 (100)	23 (100)
Race			
	Black/African-American	1 (4.3)	0 (0)
	Caucasian	21 (91.3)	23 (100)
Menopausal status			
	Pre-	0 (0)	9 (39.1)*
	Post-	23 (100)	14 (60.8)
Employment			
	Full time	16 (69.6)	14 (60.9)
	Part time	5 (21.7)	6 (26.1)
	Retired	1 (4.3)	1 (4.3)
	Unemployed	1 (4.3)	3 (8.7)
Marital status			
	Single	2 (8.7)	3 (13)
	Married	16 (69.6)	16 (69.6)
	Separated	0 (0)	1 (4.3)
	Divorced	22 (8.7)	2 (8.7)
	Widowed	1 (4.3)	0 (0)
	In relationship	2 (8.7)	0 (0)
Variable[b]	Range	BCS (mean, SD)	HC (mean, SD)
Age	38–64	53.26 (6.01)	51.87 (8.0)
Education (years)	8–24	16.35 (2.55)	17.22 (2.53)
BMI	20.4–43	27.62 (5.14)	27.65 (6.68)
MET Hours	1.63–83.72	18.34 (12.30)	21.62 (20.72)

BCS breast cancer survivor, *BMI* body mass index, *HC* healthy control, *MET* metabolic equivalent of task

[a] Chi-square or Fisher's exact test when cell counts < 5

[b] Unpaired Student's *t* test/Wilcoxon rank sum tests depending on normality/data distribution

*$p = .002$

participant's eyes in order to maximize data capture. Participants gazed at a large red dot (4.5-cm radius) on the iPad screen while completing the auditory components of the neurocognitive test battery that involved verbal responses (WAIS LNS, WMS LM I and II, F-A-S tests). Letters for the N-back test were displayed on the iPad, and the participant indicated their selections with a computer mouse. EyeWorks™ Record software (EyeTracking, Inc., 2011) was used to record the PR to the cognitive tasks at 60 Hz. Completion of the study questionnaire and the NPT took about 60 min.

Data processing

EyeWorks™ Analyze software (EyeTracking, Inc., 2011) was used to extract the PR data and calculate PR to cognitive effort (ICA) for both eyes from the raw pupil size signal. The data were cleaned by eliminating any missing values due to eye blinks or position changes prior to analyses.

Statistical analyses

Descriptive statistics were calculated for all demographic variables. Independent two-sample *t* tests or Wilcoxon rank sum tests were used to compare group scores for each self-report instrument and the NPT. The between-group effect size (Cohen's *d*) was calculated for each outcome given the relatively small sample size and to inform future studies in the cancer survivor population. Pearson correlation coefficients between mean ICA values over time and participants' self-report of cognitive function scores were calculated in addition to 95% confidence intervals. Percent missing data were calculated for the PR ICA values for each eye on each of the NPT. Participants with greater than 50% missing ICA data from one or both eyes for a specific NPT were excluded from the analyses for that NPT. The significance level was set at .05 with no control for multiple testing. Given the large number of tests conducted, the findings should be considered exploratory and confirmed with larger samples.

Table 2 Cognitive performance comparisons

NP test	BCS mean ($N = 23$)	BCS SD	HC mean ($N = 21$–23)	HC SD	*p*	*d*
FAS total	44.78	90.04	45.39	12.93	0.85	− 0.05
LNS scale	11.96	3.67	11.27	3.07	0.54	0.20
LNS long Sequence	6.04	1.22	6.19	1.08	0.71	− 0.13
LM1 scale	9.70	2.32	10.36	2.36	0.32	− 0.29
LM2 scale	10.17	2.209	10.50	2.52	0.65	− 0.14
0-back accuracy (%)	96.6	2.52	96.19	2.30	0.52	0.20
1-back accuracy (%)	96.81	3.24	95.46	3.07	0.11	0.43
2-back accuracy (%)	84.12	8.46	84.23	6.08	0.96	− 0.02

Independent Student's *t* tests or Wilcoxon rank sum tests used based on normality of distribution of the data. Cohen's *d* is the measure of effect size

BCS breast cancer survivor, *CI* confidence interval, *FAS* verbal fluency, *HC* healthy controls, *ICA* Index of Cognitive Activity, *LM* Logical Memory, *LNS* Letter Number Sequencing, *NP* neuropsychological, *PCA* perceived cognitive abilities, *PCI* perceived cognitive impairment, *SD* standard deviation

Table 3 Self-report of cognitive function

Variable	Range	BCS (mean, SD)	HC (mean, SD)	p[a]
PCI	9–72	34.09 (16.68)	58.74 (10.15)	< .0001
PCA	7–28	14.87 (6.20)	23 (3.58)	< .0001
QOL	0–16	11.7 (3.98)	14.43 (2.17)	.006
PROMIS cognition	23.3–54.6	40.76 (7.64)	31.18 (5.30)	< .0001
PROMIS ability	27–64.8	43.14 (9.18)	52.65 (8.08)	.001

BCS breast cancer survivor, *HC* healthy control, *PCA* perceived cognitive abilities, *PCI* perceived cognitive impairment, *PROMIS* Patient Reported Outcomes Measurement System, *QOL* quality of life

[a] Unpaired Student's *t* test/Wilcoxon rank sum tests depending on normality/data distribution

Results

Forty-six women participated in the study and included 23 BCS and 23 HC. The majority of BCS had stage I disease (13, 57%). Eight survivors had stage II disease (35%) and one survivor had stage III disease (4%). The mean time since completion of chemotherapy was 2.5 years (range of 9 months to 6 years) and 61% had received radiation therapy. No significant differences in demographic variables were noted between the BCS and the HC for ethnicity, race, years of education, employment or marital status, age, or activity level (Table 1 for complete breakdown of demographics). The only significant difference between the two groups was menopausal status. All the BCS were post-menopausal. Nine of the 23 HC (39%) were pre-menopausal. Statistical analyses were conducted both with and without the nine pre-menopausal controls. Statistical analyses also were conducted to assess differences between the pre- and post-menopausal HC. Given that the results did not change, results for the full sample (excluding only those missing greater than 50% of ICA data on any given NPT) are reported here.

As expected, no differences were noted between BCS and HC for performance on any of the NPT (Table 2). BCS reported significantly more issues with cognitive function on all of the self-report instruments (Table 3). A group effect for BCS was seen with PR-indexed cognitive effort (ICA) for components of all but one of the NPT (Table 4). BCS' mean ICA values were greater for the WAIS LNS (both eyes), LM1 (both eyes), LM2 (right eye), and the N-back (1-back and 2-back, right eyes) tests. The group effect for the FAS test was not significant; however, the effect sizes were large ($d = 0.56–0.59$). Significant correlation (Pearson's) was seen between PR and most self-report measures of cognitive function (Table 5). Significant correlation between self-report and PR consistently was seen with the WAIS LNS, WMS LM1 and 2, and the N-back (1-back) tests.

Table 4 Pupillary response-indexed cognitive effort (ICA) comparisons between groups

NP test	BCS ICA, mean	BCS ICA, SD	BCS, n	HC ICA, mean	HC ICA, SD	HC, n	p	d
LNS left	0.40	0.12	19	0.33	0.06	20	0.03*	0.76
LNS right	0.42	0.11	18	0.34	0.08	19	0.01*	0.84
LM1 left	0.39	0.10	21	0.33	0.03	21	0.03*	0.71
LM1 right	0.42	0.10	20	0.34	0.08	20	0.01*	0.84
LM2 left	0.37	0.11	21	0.32	0.07	21	0.10	0.52
LM2 right	0.40	0.10	20	0.33	0.08	21	0.02*	0.73
FAS left	0.37	0.10	21	0.33	0.07	20	0.08	0.56
FAS right	0.39	0.10	20	0.34	0.08	21	0.07	0.59
0-back left	0.39	0.13	19	0.40	0.09	20	0.55	0.19
0-back right	0.42	0.12	21	0.37	0.11	20	0.16	0.45
1-back left	0.38	0.13	21	0.35	0.09	22	0.33	0.30
1-back right	0.44	0.13	20	0.33	0.12	20	0.01*	0.82
2-back left	0.37	0.12	20	0.34	0.10	22	0.33	0.30
2-back right	0.42	0.13	18	0.35	0.10	20	0.047*	0.66

Independent Student's *t* tests or Wilcoxon rank sum tests based on normality of distribution of the data. Cohen's *d* is the measure of effect size.

BCS breast cancer survivor, *CI* confidence interval, *FAS* verbal fluency, *HC* healthy controls, *ICA* Index of Cognitive Activity, *LM* Logical Memory, *LNS* Letter Number Sequencing, *NP* neuropsychological, *SD* standard deviation

Asterisk indicates statistical significance at the .05 alpha level

Table 5 Pupillary response (ICA) correlation with self-report of cognitive function

	PCI			PCA			PROMIS Cognition			PROMIS Ability		
NP test	*r*	CI	*n*	*r*	CI	*n*	*r*	CI	*n*	*r*	CI	*n*
LNS left	− 0.33*	− 0.59, − 0.02	39	− 0.47*	− 0.69, − 0.19	39	0.37*	0.06, 0.61	39	− 0.38*	− 0.62, − 0.07	39
LNS right	− .047*	− 0.69, − 0.17	37	− 0.47*	− 0.69, − 0.17	37	0.46*	0.16, 0.68	37	− 0.39*	− 0.64, − 0.08	37
LM1 left	− 0.23	− 0.50, 0.08	42	− 0.32*	− 0.57, − 0.02	42	0.27	− 0.04, 0.53	42	− 0.31*	− 0.56, − 0.01	42
LM1 right	− 0.39*	− 0.62, − 0.09	40	− 0.35*	− 0.59, − 0.04	40	0.35*	0.04, 0.59	40	− 0.28	− 0.54, 0.04	40
LM2 left	− 0.19	− 0.47, 0.12	42	− 0.31*	− 0.56, − 0.01	42	0.20	− 0.11, 0.47	42	− 0.25	− 0.51, 0.06	42
LM2 right	− 0.44*	− 0.66, − 0.16	41	− 0.47*	− 0.68, − 0.19	41	0.41*	0.12, 0.64	41	− 0.39*	− 0.62, − 0.10	41
FAS left	− 0.21	− 0.49, 0.11	41	− 0.30	− 0.56, 0.004	41	0.28	− 0.03, 0.54	41	− 0.27	− 0.53, 0.04	41
FAS right	− 0.32*	− 0.57, − 0.01	41	− 0.34*	− 0.58, − 0.03	41	0.31*	0.01, 0.57	41	− 0.30	− 0.55, 0.01	41
0-back left	− 0.10	− 0.41, 0.22	39	− 0.22	− 0.50, 0.10	39	0.09	− 0.23, 0.40	39	− 0.15	− 0.45, 0.17	39
0-back right	− 0.23	− 0.50, 0.08	41	− 0.30	− 0.55, 0.01	41	0.21	− 0.11, 0.48	41	− 0.24	− 0.51, 0.07	41
1-back left	− 0.18	− 0.45, 0.13	43	− 0.19	− 0.46, 0.12	43	0.11	− 0.20, 0.40	43	− 0.15	− 0.43, 0.15	43
1-back right	− 0.45*	− 0.67, − 0.16	40	− 0.36*	− 0.61, − 0.06	40	0.34*	0.03, 0.59	40	− 0.37*	− 0.61, − 0.07	40
2-back left	− 0.19	− 0.46, 0.13	42	− 0.18	− 0.4597, 0.13	42	0.11	− 0.20, 0.40	42	− 0.14	− 0.43, 0.17	42
2-back right	− 0.31	− 0.57, 0.01	38	− 0.33	− 0.59, − 0.02	38	0.30	− 0.02, 0.56	38	− 0.25	− 0.53, 0.07	38

CI confidence interval, *FAS* verbal fluency, *HC* healthy controls, *ICA* Index of Cognitive Activity (pupil dilation), *LM* Logical Memory, *LNS* Letter Number Sequencing, *NP* neuropsychological, *PCA* perceived cognitive abilities, *PCI* perceived cognitive impairment, *PROMIS* Patient Reported Outcomes Measurement System, *SD* standard deviation

Asterisk indicates statistical significance at the .05 alpha level

Conclusions

During NP testing, BCS in this pilot study demonstrated significantly greater pupil dilation (ICA) for tests of auditory, short-term, and delayed working memory despite performances that commensurate with those of HC. Consistent with the previous literature, BCS reported significantly more issues with cognitive function than HC [13]. These results corroborate the phenomenon of a disparity between self-report of cognitive dysfunction and actual cognitive performance on selected NPT. The study participants were well-educated and thus likely had significant cognitive reserve which facilitated normal cognitive performance despite the perception of increased cognitive effort.

Correlation between PR-indexed cognitive effort and self-report of cognitive function also was demonstrated. Earlier research has shown that self-report of cognitive dysfunction precedes changes in performance on NPT [33]. Self-report coincides with demonstration of increased cognitive effort as evidenced by changes in neural activation measured by functional neuroimaging [33]. Future research to prospectively compare changes in PR-indexed cognitive effort to changes in brain structure, neural activation, and functional connectivity would yield important information about the early sensitivity of PR to specific cognitive domains affected by cancer and cancer treatment-related cognitive dysfunction and potential use as a less expensive, clinically accessible measure.

Interestingly, some differences were noted between sensitivity of PR to cognitive effort for the right and left eyes. Overall, increased pupillary dilation was noted for the right eye, although the BCS group demonstrated significantly greater pupillary dilation in both eyes for the WAIS LNS and LM 1 (both tests specific to the cognitive domains of working memory and auditory memory recall). Brain hemispheric differences may explain these findings. Exploration of the correlation of PR to functional magnetic resonance imaging (fMRI)-indexed activation of specific cognitive domains and differences in functional connectivity may shed light on the differences in PR between the right and left eyes [34].

These preliminary study findings indicate that PR measurement reflects the increased amount of cognitive effort expended by BCS compared to HC. Our findings also indicate correlation between PR-indexed cognitive effort and both self-report and objective measures of cognitive function.

Limitations

Generalization of findings is limited by the small sample size and cross-sectional design. The groups were well-matched for age and education level. Although the healthy controls group included some pre-menopausal women (matching for age did not account for the treatment-induced menopause for younger breast cancer survivors), this difference did not affect the statistical

analyses. Very few participants were missing > 50% data for the ICA values (range from three to nine participants across the NPT for the right or left eyes). This level of missing data is expected due to individual differences in eye blinks, saccadic eye movements, and head position during scanning and exclusion of test results with < 50% missing ICA data is conservative compared to some other studies [35–38]. The current study did not include NPT for the visual spatial ability (Rey-Osterrieth Complex Figure test), processing speed (Trail Making A), and the task-switching components of executive function (Trail Making B), due to logistical challenges for remote eye tracking during these tests. The cross-sectional study design prevented comparisons to baseline cognitive effort prior to receiving chemotherapy.

Clinical implications

These study results suggest that PR is sensitive to cognitive effort across a variety of NPT and demonstrated good correlation with self-report of cognitive function. The portability, affordability, and "real-time" aspects of PR assessment are attractive for potential use in the clinic setting to assess cognitive function in BCS. More work is needed with a larger sample to confirm these results. Prospective study of the sensitivity of PR in this population is needed to demonstrate sensitivity to changes in cognitive function over time. Prospective investigation of PR in conjunction with fMRI-indexed measures domain-specific cognitive effort, and changes in functional connectivity would provide valuable comparisons of the sensitivity of the two measures of cognitive effort. Future expansion of the research to include investigation of PR sensitivity to additional cognitive domains and in other cancer populations also is needed.

Funding information The study was funded by the University of Kansas Medical Center Frontiers Pilot & Collaborative Studies Award.

Compliance with ethical standards

Approval from the University of Kansas Human Subjects Committee was obtained, and all procedures were performed in accordance with institutional ethical standards and the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors have no financial relationships to disclose. The first author and Primary Investigator for the study have full control of all primary data. However, data sharing agreement execution would be necessary if the journal requests data review.

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