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Neurophysiologic and ophthalmic markers of chemotherapy-related cognitive impairment in patients diagnosed with hematologic cancer: A feasibility study

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ABSTRACT

Background: Biomarkers of chemotherapy-related cognitive impairment (CRCI) in hematologic cancer are understudied and underdeveloped. We evaluated the feasibility of using ophthalmic and neurophysiologic markers to assess CRCI in hematologic cancer.

Methods: Hematologic cancer patients either receiving (Ctx+) or not receiving (Ctx−) chemotherapy were recruited from a tertiary medical center. Demographically-matched healthy controls (HC) were also recruited. Ctx+ participants completed the following study visits: (1) after diagnosis but prior to chemotherapy (baseline); (2) after one treatment cycle (one-month post-baseline); and (3) after three treatment cycles (three-months post-baseline). Comparison subjects completed assessments at similar intervals. Participants completed: (1) neuropsychological assessments of attention and executive function; (2) neurophysiologic assessments of control over spatial attention and working memory; and (3) ophthalmic assessments of contrast sensitivity and optical coherence tomography (OCT).

Results: We enrolled 45 participants (15 per group), and 30 participants (Ctx+ = 8; Ctx− = 10; HC = 12) completed all study visits. Ctx+ participants performed worse than HC participants on neuropsychological measures of attention and executive function. Both Ctx+ and Ctx− participants showed changes in neurophysiologic measures of control over spatial attention that differed from HC participants. Ctx+ participants showed chemotherapy-related declines in contrast sensitivity that were predicted by OCT retinal nerve fiber layer thickness (RNFL) changes. Changes in neurophysiologic measures of control over spatial attention were also predicted by OCT RNFL changes.

Conclusion: We demonstrated the feasibility of using ophthalmic and neurophysiologic markers as rapid and non-invasive measures that may be useful for tracking CRCI in hematologic cancer.

1. Introduction

Chemotherapy-related cognitive impairment (CRCI) affects up to 75% of cancer survivors [1], and impacts multiple cognitive domains, including processing speed, attention, working memory, and executive function [2,3]. CRCI is associated with brain network dysfunction, primarily within frontal and parietal cortices [4,5]. Our knowledge of CRCI across malignancies is limited, however, because the majority of studies have evaluated breast cancer survivors [1].

CRCI in patients with hematological cancers is severely understudied [6]. One longitudinal study found new onset cognitive impairment in 53.3% of patients undergoing chemotherapy compared to baseline performance [7]. Another longitudinal study found dose-dependent declines in cognitive performance [8]. Critically, these studies

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lacked appropriate comparison groups to dissociate contributions from cancer pathophysiology and treatment toxicity.

Positron emission tomography (PET) studies have evaluated metabolic brain activity in separate groups of pre- and post-chemotherapy lymphoma patients [9,10]. Chemotherapy-related reductions of metabolic activity primarily in prefrontal regions predicted executive function performance [9]. The same authors parcellated brain regions into the central executive network (CEN) and dorsal attention network (DAN) [10]. Classification algorithms discriminated chemotherapy from non-chemotherapy patients most accurately (80%) when both DAN and CEN were considered together. Classification accuracy was lower, by contrast, when DAN (50%) or CEN (65%) were considered separately. Critically, no studies have longitudinally evaluated chemotherapy-related changes in functional activity associated with DAN and CEN. It therefore remains unclear how cancer pathophysiology and treatment toxicity distinctly contribute to DAN and CEN changes.

CRCI biomarker development has focused on immunologic and genetic markers [11,12], whereas neuroimaging markers have been less robust. The retina, being an outpost of the brain, offers more rapid and non-invasive markers for assessing neuronal structure and function. Optical coherence tomography (OCT) provides micron-level resolution of neurosensory retinal structures. Post-treatment cancer patients show sub-clinical reductions in retinal nerve fiber layer (RNFL) thickness [13,14], though OCT studies have evaluated neither hematologic cancer patients nor CRCI. Elucidating the relationship between retinal and cortical degeneration promises to further develop neural biomarkers of CRCI.

Here, we sought to evaluate the feasibility of combing neurophysiologic and ophthalmic markers to assess CRCI in patients receiving chemotherapy for hematologic cancer. To this end, we developed a study design that longitudinally assessed hematologic cancer patients receiving chemotherapy, and included patients not receiving chemotherapy and healthy controls as comparisons. Our primary goal was to assess chemotherapy-related changes in task-related neural activity to corroborate previous PET studies [9,10]. To this end, we measured neurophysiologic correlates of control over spatial attention and working memory, which are governed by the DAN [15–18] and CEN [19–21], respectively. During two computer-based cognitive tasks, we recorded scalp electroencephalography (EEG) to measure: (1) the N2pc event-related potential (ERP) component [22], a neurophysiologic correlate of control over spatial attention [23,24]; and (2) the contralateral delay activity (CDA) ERP component, a neurophysiologic correlate of control over working memory [25–27]. Prior to initiating treatment, patients from this sample showed larger N2pc and CDA amplitudes relative to healthy controls [28], indicating cancer-related impairments in DAN and CEN function. Our secondary goal was to assess chemotherapy-related changes in retinal structure and function by evaluating OCT RNFL thickness and visual contrast sensitivity, respectively. Results obtained from this feasibility study could provide preliminary insights into whether changes in neurophysiologic and ophthalmic markers could be used to assess CRCI in cancer patients.

2. Methods

2.1. Study design and participants

A longitudinal observational pilot study was conducted at the University of Nebraska Medical Center (UNMC) between September 2016 and November 2017. The study was conducted in accordance with the Declaration of Helsinki following approval by the Institutional Review Board (IRB). All participants provided IRB approved informed consent.

Hematologic cancer patients were recruited from the UNMC Fred and Pamela Buffett Cancer Center. HC participants were recruited from an existing research registry in the UNMC Department of Neurological Sciences. Inclusion criteria for all groups were: (1) 19–80 years of age; and (2) self-reported normal or corrected-to-normal vision. Exclusion criteria for both groups were: (1) previous cancer diagnosis, (2) previous radiotherapy or chemotherapy, and (3) baseline mild cognitive impairment (MMSE score $<$ 25).

Patients were recruited into one of two cohorts: (1) patients scheduled to receive chemotherapy (Ctx+ group); and (2) patients receiving best supportive care or no treatment (Ctx− group). We recruited a third cohort of demographically-matched (age: ± 5 years; education: ± 5 years; gender) HC participants. Participants in the Ctx+ group (or comparison groups) completed three study visits at the following intervals: (1) after diagnosis but prior to chemotherapy treatment (or baseline); (2) after one treatment cycle (or one-month post-baseline); and (3) after three treatment cycles (or three-months post-baseline).

2.2. Neuropsychological assessment

Four cognitive assessments were administered: Trail Making Test (Trails A/B) [29], Golden Stroop [30], Paced Auditory Serial Addition Task (PASAT) [31], and Useful Field of View (UFOV) [32]. These assessments provide gold-standard measures of processing speed (Trails A), attention (PASAT, UFOV), and executive function (Trails B, Stroop). Outcome measures were completion time for Trails A/B, total correct for Stroop sub-tasks (Stroop-W, Stroop-C, Stroop-CW) and interference score (Stroop-I) for Stroop performance, number of trials attempted and correct for PASAT, and processing time for UFOV sub-tasks (Divided Attention, Selective Attention).

2.3. Cognitive electrophysiology

Participants completed two computer-based cognitive tasks. During a modified visual search task [22,33], participants were instructed to locate a target object within each search display. Prior to 50% of search displays, a task-irrelevant cue that was either similar (*High-Similarity* condition) or dissimilar (*Low-Similarity* condition) to the target object was briefly presented to capture attention. Performance costs incurred by task-irrelevant cues were estimated as *d'*. During a modified change detection task [25,34], participants were instructed to remember either one or three target objects presented within each memory display. Following a brief delay period, participants were randomly tested on a single target object. On 50% of trials, task-irrelevant objects dissimilar to target objects were presented within memory displays. *Load effects* were estimated as performance costs incurred by increasing memory load. *Filter effects* were estimated as performance costs incurred by task-irrelevant objects.

EEG was recorded using a Neuroscan NuAmps system [28,35]. ERP epochs were extracted after the presentation of each stimulus display with a pre-stimulus baseline period of 200 ms. Contralateral (or ipsilateral) waveforms were created by averaging ERP epochs from right posterior electrodes when the stimulus cue was presented in the left (or right) visual hemifield, and from left posterior electrodes when the stimulus cue was presented in the right (or left) visual hemifield. Difference waveforms were created for each electrode pair by subtracting ipsilateral waveforms from contralateral waveforms. For the visual search task, ERP waveforms were measured 0–400 ms after cue display onset to determine the presence of N2pc activity in both *Low-Similarity* and *High-Similarity* conditions. Larger N2pc amplitudes reflect larger spatial shifts of attention towards the task-irrelevant cue. For the change detection task, ERP waveforms were measured 0–1000 ms after memory display onset to determine the presence of CDA activity. We calculated: (1) CDA_{Load} as changes in CDA amplitude as a function of increasing memory load, where larger CDA_{Load} values reflect larger load-dependent increases in CDA amplitude; and (2) CDA_{Filter} as Filter-1 CDA amplitudes minus Load-1 CDA amplitudes, where larger CDA_{Filter} values reflect larger filter-related increases in CDA amplitude.

2.4. Visuo-retinal assessment

Visual acuity and contrast sensitivity were assessed using retro-illuminated (1095 cd/m2) 100%, 5%, and 2.5% contrast vision charts presented on standard light box (Precision Vision; La Salle, Illinois) in a dark room. Patients were seated 4 m from the charts during testing and used their available refractive correction. Logarithm of minimum angle of resolution (logMAR) values were assigned for left (OS), right (OD), and both (OU) eyes for visual acuity (100%) and contrast sensitivity (5%, 2.5%) charts.

Cirrus HD-OCT (Carl Zeiss Meditec Inc.) acquired scans of the retina and optic nerve using the Macular Cube and Optic Disc Cube protocols, respectively. We obtained global measurements of the RNFL and ganglion cell layer (GCL). Good quality scans with appropriate centering, clear images, and signal strength > 6 were included in analyses.

2.5. Statistical analysis

Statistical analyses were performed with SAS Studio 3.6 (SAS Institute Inc.). Categorical data were descriptively summarized using frequency and percentage tables. Numeric data were descriptively summarized using means and standard deviations. Univariate graphs were created for predictor (e.g. age, education) and response variables (e.g. ERP amplitude) to investigate distributional properties. One-way ANOVA was performed to assess between-group differences in age, education, and gender. Chi-squared tests were performed to assess between-group differences in gender.

Between-group differences and within-group changes in repeated measures were assessed using linear mixed models. Repeated measures were modeled using a compound symmetry covariance structure. Kenward-Roger degrees of freedom corrections were used to account for missing data [36]. Omnibus statistics were evaluated for effects of group and visit, and group-by-visit interactions. Post-hoc within- and between-group contrasts were assessed by comparing model-derived least square means (LSM). Modeling procedures were further modified to determine whether changes in outcome measures were associated with changes in retinal markers (e.g. OCT measures). Within-subject differences in all outcome measures were estimated between T1-T2 and T2-T3 time points. Retinal markers were included in modeling procedures, as outlined above. Statistical significance was set to the standard $p < .05$ level. We also estimated standardized effect sizes [37] (Cohen's d) for main effects and reported those that exceeded a medium effect size of 0.5.

3. Results

3.1. Study participants

Participants were 60.8 ± 14.5 years of age (range: 22–80 years), 47% male, 98% Caucasian, 86% right-handed, 64% married, and had 13.9 ± 1.5 years of education (Table 1). Study groups were balanced on age ($F_{(2,42)} = 0.30$, $p = .74$), gender ($\chi^2_{(2)} = 0.53$, $p = .77$), education ($F_{(2,40)} = 1.01$, $p = .37$), handedness ($\chi^2_{(2)} = 0.93$, $p = .63$), race ($\chi^2_{(2)} = 2.05$, $p = .36$), and marital status ($\chi^2_{(2)} = 1.33$, $p = .51$).

Ctx+ patients were primarily diagnosed with non-Hodgkin lymphoma (NHL; 67%) and acute myeloid leukemia (20%), and were recruited a median of 11 days after diagnosis (range: 0–125 days); longer delays between diagnosis and chemotherapy initiation were seen in low-grade NHL patients who were initially under active surveillance. Ctx− patients were primarily diagnosed with NHL (40%) and myeloid dysplastic syndrome (40%), and were recruited a median of 11.6 months after diagnosis (range: 0–70.1 months).

Ctx+ patients received a regimen comprised primarily of one or more of the following agents: doxorubicin (67%), cyclophosphamide (58%), vincristine (58%), rituximab (58%), decitabine (25%), and prednisone (58%) (Table 1).

3.2. Study completion

30 (67%) study participants completed all study visits. Patients who withdrew from or completed the study did not differ with respect to age ($F_{(1,43)} = 1.55$, $p = .22$), gender ($\chi^2_{(1)} = 0.40$, $p = .53$), education ($F_{(1,41)} = 1.99$, $p = .17$), marital status ($\chi^2_{(1)} = 0.19$, $p = .66$), or MMSE score ($F_{(1,41)} = 0.33$, $p = .57$). Of the 15 participants who withdrew from the study, 7 were Ctx+ patients (47% group withdraw rate), 5 were Ctx− patients (33% group withdraw rate), and 3 were HCs (20% group withdraw rate). No significant difference in withdraw rate was observed between groups ($\chi^2_{(2)} = 2.45$, $p = .29$). Reasons for study withdrawal were time constraints ($n = 5$), travel constraints ($n = 2$), stroke (n = 2), pain ($n = 1$), hospice care (n = 1), started chemotherapy (n = 1), receiving treatment elsewhere (n = 1), and stopped responding to calls (n = 2).

3.3. Neuropsychological assessment

Descriptive statistics for all assessments are provided in Table 2. Analyses revealed a trending effect of group on Stroop-CW ($F_{(2,41.5)} = 2.82$, $p = .071$; Cohen's d = 0.51) and Stroop-I ($F_{(2,41.7)} = 2.86$, $p = .068$; Cohen's d = 0.51). Post-hoc comparisons revealed better performance in HC relative to Ctx+ participants for both Stroop-CW ($t_{(41.8)} = -2.36$, $p = .023$) and Stroop-I ($t_{(42.2)} = 2.39$, $p = .021$). In addition, we observed a significant group-by-visit interaction on PASAT Attempts ($F_{(4,53.8)} = 2.73$, $p = .038$; Cohen's d = 0.43). Post-hoc comparisons revealed: (1) higher PASAT in HC relative to Ctx+ groups at T1 ($t_{(39.5)} = -2.16$, $p = .037$) and T2 ($t_{(43.6)} = -2.41$, $p = .020$); and (2) an increase in Ctx+ group from T2 to T3 ($t_{(54.1)} = 2.58$, $p = .0126$), whereas no significant changes were observed across other groups and timepoints.

3.4. Cognitive electrophysiology

Analyses of behavioral data revealed a trending effect of group on low-similarity d' ($F_{(2,33.1)} = 2.58$, $p = .09$; Cohen's d = 0.54). Post-hoc comparisons revealed smaller d' values were observed in Ctx+ relative to Ctx− groups ($t_{(32.5)} = -2.27$, $p = .030$). Analyses of ERP data revealed a significant group-by-visit interaction on high-similarity N2pc amplitudes ($F_{(4,56.1)} = 3.50$, $p = .013$; Cohen's d = 0.48). Post-hoc comparisons revealed an increase in high-similarity N2pc amplitudes in HC participants from T1 to T3 ($t_{(57.2)} = -3.0$, $p = .004$), whereas no differences were observed between and within other groups.

3.5. Vision assessment

Ctx+ patients showed: (1) declines in both 5% and 2.5% contrast sensitivity across left (OS) and right (OD) eyes between T1 and both T2 and T3; (2) RNFL thickening (> 4 μm) between T1 and T2; and (3) RNFL thinning (> 7 μm) between T2 and T3. We assessed the relationship between changes in contrast sensitivity from T1-to-T2 timepoints and RNFL thickness from T2-to-T3 timepoints while accounting for group. Changes in RNFL thickness were associated with changes in contrast sensitivity for OS 5% ($F_{(1,13)} = 7.99$, $p = .014$; Cohen's d = 1.38; β = 0.010 ± 0.004), OD 5% ($F_{(1,13)} = 3.39$, $p = .089$; Cohen's d = 0.74; β = 0.011 ± 0.006), and OD 2.5% ($F_{(1,13)} = 11.48$, $p = .005$; Cohen's d = 1.41; β = 0.014 ± 0.004). Furthermore, we observed an effect of group on changes in contrast sensitivity for OS 5% ($F_{(2,13)} = 3.93$, $p = .046$; Cohen's d = 1.2), OS 2.5% ($F_{(2,13)} = 3.09$, p-0.080; Cohen's d = 1.0), OD 5% ($F_{(2,13)} = 2.68$, $p = .106$; Cohen's d = 0.75), and OD 2.5% ($F_{(2,13)} = 3.02$, $p = .084$; Cohen's d = 0.86). Post-hoc comparisons revealed larger contrast sensitivity reductions in: (1) Ctx+ relative to Ctx− participants in OS 5% ($t_{(13)} = 2.66$, $p = .0196$), OS 2.5% ($t_{(13)} = 2.36$, $p = .035$), and OD 2.5% ($t_{(13)} = 2.56$, $p = .083$); and (2) Ctx+ relative to HC participants in OS 5% ($t_{(13)} = 2.03$, $p = .063$), OS 2.5% ($t_{(13)} = 1.81$, $p = .094$), OD 5%

Table 1
Study sample characteristics. Continuous data are presented as means and standard deviations: M ± SD; Categorical data are presented as frequencies and percentages: N (%).

	CTX+ (*n* = 15)		CTX− (n = 15)		HC (n = 15)	
	N (%)	*M* ± SD	*N (%)*	*M* ± SD	*N (%)*	*M* ± SD
Demographics						
Age		59.3 ± 15.2		63.2 ± 10.9		60.0 ± 16.5
Gender (% Males)	8 (53)		6 (40)		7 (47)	
Years of Education		13.9 ± 1.7		13.5 ± 1.3		14.3 ± 1.6
Diagnosis						
NHL	10 (67)		6 (40)			
MDS	1 (7)		6 (40)			
AML	3 (20)		0 (0)			
CLL	0 (0)		2 (13)			
ALL	1 (7)		0 (0)			
MM	0 (0)		1 (7)			
Chemotherapy protocol						
R-CHOP	5					
Decitabine	3					
CHOP	1					
BR	1					
EPOCH-R	1					
ABVD	1					

(Ctx+ = Chemotherapy patient group; Ctx− = non-chemotherapy patient group; HC = healthy control group; NHL = non-Hodgkin lymphoma; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; ALL = acute lymphoblastic leukemia; MM = multiple myeloma; CHOP = Cyclophosphamide/Doxorubicin/Vincristine/Prednisone; R-CHOP = Rituximab/CHOP; BR = Rituximab/Bendamustine; EPOCH-R = Etoposide/Prednisone/Vincristine/Cyclophosphamide/Doxorubicin/Rituximab; ABVD = Doxorubicin/Bleomycin/Vinblastine/Dacarbazine).

($t_{(13)} = 2.29$, $p = .039$), and OD 2.5% ($t_{(13)} = 2.28$, $p = .034$).

Next, we evaluated associations between changes in ophthalmic and neurophysiologic measures. Changes in high-similarity N2pc amplitudes were associated with changes in RNFL thickness in both OS ($F_{(1,16)} = 16.18$, $p = .001$; Cohen's d = 1.95; $\beta = -0.081 \pm 0.020$) and OD ($F_{(1,15)} = 4.04$, p = .063; Cohen's d = 1.01; $\beta = -0.091 \pm 0.045$) measurements.

4. Conclusions

This is the first study to assess the feasibility of longitudinally evaluating both neurophysiologic and ophthalmic markers of CRCI in hematological cancer patients. Neurophysiologic markers of brain networks underlying spatial attention and working memory revealed the potential to dissociate patterns of activity between hematologic cancer patients and healthy comparisons. Ophthalmic markers revealed the potential to detect chemotherapy-related reductions in visual function that may be sensitive to changes in retinal structure. In addition, the design of this feasibility study overcame limitations of previous studies by including appropriate comparison groups and more rigorous cognitive assessments. Together, this feasibility study demonstrates that these measures may provide a novel platform for further investigating CRCI in hematologic cancer patients.

We assessed the feasibility of tracking chemotherapy-related changes in neurophysiologic correlates of control over spatial attention and working memory by measuring N2pc and CDA amplitudes, respectively. In previous work, we demonstrated larger N2pc and CDA amplitudes in both cancer groups prior to initiating treatment relative to healthy comparisons [28]. Here, N2pc amplitudes, reflecting brain activity within the DAN [15–18], revealed significant differences between hematologic cancer patients and healthy comparisons over time. Specifically, we observed a decrease in N2pc amplitudes across study visits in both cancer groups whereas healthy comparisons showed an increase in N2pc amplitudes. In contrast, CDA amplitudes, reflecting brain activity within the CEN [19–21], showed no reliable differences between hematologic cancer patients and comparisons over time. Importantly, however, the medium effect size (Cohen's d = 0.36) observed in the omnibus interaction between group and study visit on CDA amplitudes warrants further investigation in a larger fully powered study. These preliminary results demonstrate the potential to detect a clear dissociation in the pattern of DAN and CEN activity between hematologic cancer patients and healthy comparisons. Future large-scale studies will allow for further testing of how dysregulation of DAN and CEN activity following chemotherapy may influence neurophysiological underpinnings of control over spatial attention and working memory.

Our preliminary neurophysiologic results may be considered in the context of previous PET studies of CRCI in hematologic cancer patients [9,10]. For example, prior PET studies used pattern classification methods to discriminate between chemotherapy treated and untreated lymphoma patients, and found chemotherapy-related differences in metabolic activity within the DAN. When evaluating metabolic activity across all brain regions within the DAN, by contrast, no difference in metabolic activity was observed between chemotherapy and non-chemotherapy groups. In the current work, chemotherapy and non-chemotherapy hematologic cancer patients showed similar patterns in N2pc amplitudes, a neurophysiologic marker of DAN function, which were dissociable from healthy comparisons. It remains unclear how changes in N2pc amplitudes are associated with DAN network activity, per se, and whether patterns of activity differ across distributed brain regions within the DAN.

We assessed the feasibility of tracking chemotherapy-related changes in retinal structure and function by measuring OCT RNFL thickness and contrast sensitivity, respectively. Our preliminary findings revealed differences between patients receiving chemotherapy and both non-chemotherapy and healthy comparison groups. Specifically, patients receiving chemotherapy showed a decline in contrast sensitivity that was unobserved in both comparison groups. Furthermore, chemotherapy-related declines in contrast sensitivity were associated with changes in OCT RNFL thickness, where larger reductions in contrast sensitivity were associated with larger increases in RNFL thickness. The association between chemotherapy-related RNFL thickening and changes in both contrast sensitivity and high-similarity N2pc amplitudes may be related to an initial inflammatory response observed during chemotherapy [38,39]. Previous studies in other cancer populations have shown chemotherapy-related reductions in RNFL thickness [13,14], suggestive of neuronal loss. Differences between studies are likely due to measurement times: previous studies collected OCT

Table 2
Study outcome measures. Data are presented as means and standard deviations: M ± SD.

	CTX+			CTX−			HC		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
Vision assessment									
OD									
100% Contrast	0.025 ± 0.126 (*n* = 8)	−0.005 ± 0.127 (*n* = 8)	0.060 ± 0.085 (*n* = 8)	0.051 ± 0.116 (*n* = 11)	0.043 ± 0.113 (*n* = 8)	0.016 ± 0.147 (*n* = 9)	0.042 ± 0.091 (*n* = 12)	0.022 ± 0.080 (*n* = 11)	−0.003 ± 0.085 (*n* = 12)
5% Contrast	0.340 ± 0.145 (*n* = 9)	0.380 ± 0.157 (*n* = 8)	0.400 ± 0.077 (*n* = 8)	0.393 ± 0.175 (*n* = 11)	0.358 ± 0.170 (*n* = 9)	0.427 ± 0.208 (*n* = 9)	0.397 ± 0.091 (*n* = 12)	0.387 ± 0.090 (*n* = 11)	0.327 ± 0.104 (*n* = 12)
2.5% Contrast	0.504 ± 0.156 (*n* = 9)	0.551 ± 0.095 (*n* = 7)	0.575 ± 0.121 (*n* = 8)	0.580 ± 0.237 (*n* = 11)	0.591 ± 0.249 (*n* = 9)	0.556 ± 0.242 (*n* = 9)	0.578 ± 0.101 (*n* = 12)	0.544 ± 0.114 (*n* = 11)	0.508 ± 0.150 (*n* = 12)
RNFL Thickness	93.6 ± 17.8 (*n* = 9)	98.4 ± 14.0 (*n* = 7)	89.3 ± 10.0 (*n* = 7)	88.9 ± 11.8 (*n* = 9)	91.1 ± 7.9 (*n* = 7)	91.5 ± 7.9 (*n* = 8)	87.1 ± 9.1 (*n* = 12)	86.6 ± 9.4 (*n* = 11)	89.0 ± 8.5 (*n* = 11)
GCL Thickness	71.6 ± 23.0 (*n* = 9)	79.7 ± 5.0 (*n* = 7)	76.7 ± 8.1 (*n* = 7)	77.6 ± 5.6 (*n* = 10)	77.6 ± 5.2 (*n* = 7)	79.5 ± 4.5 (*n* = 8)	76.6 ± 7.8 (*n* = 13)	76.4 ± 7.5 (*n* = 12)	77.5 ± 6.5 (*n* = 11)
OS									
100% Contrast	0.030 ± 0.128 (*n* = 8)	0.080 ± 0.145 (*n* = 8)	0.073 ± 0.114 (*n* = 8)	0.169 ± 0.352 (*n* = 11)	0.175 ± 0.343 (*n* = 8)	0.120 ± 0.342 (*n* = 9)	0.023 ± 0.124 (*n* = 12)	0.000 ± 0.089 (*n* = 11)	0.007 ± 0.114 (*n* = 12)
5% Contrast	0.367 ± 0.133 (*n* = 9)	0.388 ± 0.109 (*n* = 8)	0.418 ± 0.098 (*n* = 8)	0.551 ± 0.320 (*n* = 11)	0.487 ± 0.342 (*n* = 9)	0.478 ± 0.271 (*n* = 9)	0.350 ± 0.113 (*n* = 12)	0.349 ± 0.107 (*n* = 11)	0.320 ± 0.099 (*n* = 12)
2.5% Contrast	0.464 ± 0.193 (*n* = 9)	0.515 ± 0.148 (*n* = 8)	0.558 ± 0.144 (*n* = 8)	0.676 ± 0.263 (*n* = 11)	0.638 ± 0.325 (*n* = 9)	0.571 ± 0.271 (*n* = 9)	0.488 ± 0.099 (*n* = 12)	0.500 ± 0.110 (*n* = 11)	0.478 ± 0.144 (*n* = 12)
RNFL Thickness	93.2 ± 15.9 (*n* = 9)	97.7 ± 14.7 (*n* = 7)	90.9 ± 6.0 (*n* = 7)	85.0 ± 10.4 (*n* = 9)	87.3 ± 10.8 (*n* = 8)	91.0 ± 10.1 (*n* = 9)	84.6 ± 9.9 (*n* = 11)	82.8 ± 11.0 (*n* = 11)	84.3 ± 11.0 (*n* = 9)
GCL Thickness	77.6 ± 6.5 (*n* = 9)	79.3 ± 5.5 (*n* = 7)	78.4 ± 4.8 (*n* = 7)	77.5 ± 6.9 (*n* = 11)	76.8 ± 7.0 (*n* = 9)	79.0 ± 6.9 (*n* = 9)	76.6 ± 8.1 (*n* = 12)	76.3 ± 7.9 (*n* = 11)	77.6 ± 7.8 (*n* = 9)
Neuropsych. Assessment									
Trails A	31.9 ± 14.6 (*n* = 14)	26.2 ± 8.6 (*n* = 9)	24.0 ± 8.2 (*n* = 8)	27.6 ± 8.4 (*n* = 14)	22.0 ± 6.6 (*n* = 11)	25.5 ± 12.2 (*n* = 10)	28.5 ± 11.5 (*n* = 15)	24.8 ± 11.7 (*n* = 13)	24.3 ± 8.5 (*n* = 12)
Trails B	95.4 ± 78.8 (*n* = 14)	82.8 ± 49.9 (*n* = 9)	57.6 ± 11.5 (*n* = 8)	68.6 ± 20.2 (*n* = 14)	68.3 ± 28.9 (*n* = 11)	55.5 ± 18.4 (*n* = 10)	69.0 ± 38.3 (*n* = 15)	74.7 ± 49.1 (*n* = 13)	54.8 ± 15.4 (*n* = 11)
Stroop-W	91.4 ± 13.4 (*n* = 14)	98.0 ± 10.0 (*n* = 9)	100.3 ± 5.8 (*n* = 8)	91.0 ± 12.4 (*n* = 14)	95.5 ± 11.9 (*n* = 11)	97.5 ± 10.1 (*n* = 10)	95.5 ± 17.5 (*n* = 15)	98.7 ± 18.2 (*n* = 13)	96.7 ± 21.3 (*n* = 12)
Stroop-C	64.1 ± 12.9 (*n* = 14)	68.7 ± 13.7 (*n* = 9)	67.3 ± 17.2 (*n* = 8)	71.7 ± 14.6 (*n* = 13)	74.7 ± 4.6 (*n* = 10)	79.7 ± 9.3 (*n* = 9)	71.5 ± 13.7 (*n* = 15)	73.0 ± 14.7 (*n* = 13)	73.7 ± 17.1 (*n* = 12)
Stroop-CW	27.7 ± 12.6 (*n* = 14)	31.6 ± 14.1 (*n* = 9)	37.6 ± 12.5 (*n* = 8)	34.0 ± 10.5 (*n* = 13)	40.7 ± 11.3 (*n* = 10)	41.7 ± 10.9 (*n* = 9)	37.1 ± 14.0 (*n* = 15)	42.8 ± 12.9 (*n* = 13)	45.1 ± 13.7 (*n* = 12)
Stroop-I	9.7 ± 10.5 (*n* = 14)	8.5 ± 12.1 (*n* = 9)	2.1 ± 6.9 (*n* = 8)	5.8 ± 10.9 (*n* = 13)	1.1 ± 9.4 (*n* = 10)	2.2 ± 9.6 (*n* = 9)	3.6 ± 11.4 (*n* = 15)	−1.0 ± 8.4 (*n* = 13)	−3.4 ± 7.3 (*n* = 12)
PASAT Attempts	20.3 ± 6.8 (*n* = 10)	20.4 ± 9.2 (*n* = 7)	25.0 ± 6.8 (*n* = 7)	24.0 ± 4.8 (*n* = 13)	25.1 ± 5.7 (*n* = 11)	22.9 ± 6.5 (*n* = 10)	26.6 ± 8.1 (*n* = 15)	27.5 ± 8.8 (*n* = 13)	29.4 ± 6.1 (*n* = 11)
PASAT Correct	17.9 ± 7.1 (*n* = 10)	18.9 ± 9.3 (*n* = 7)	23.0 ± 7.7 (*n* = 7)	21.6 ± 5.3 (*n* = 13)	22.8 ± 6.0 (*n* = 11)	20.5 ± 7.6 (*n* = 10)	23.9 ± 8.5 (*n* = 15)	25.5 ± 9.0 (*n* = 13)	27.3 ± 6.4 (*n* = 11)
UFOV Processing Speed	76.3 ± 158.9 (*n* = 9)	22.1 ± 2.5 (*n* = 8)	23.3 ± 0.1 (*n* = 7)	24.1 ± 7.2 (*n* = 13)	23.0 ± 2.3 (*n* = 11)	22.0 ± 2.8 (*n* = 10)	21.3 ± 3.0 (*n* = 15)	23.3 ± 1.3 (*n* = 13)	21.6 ± 3.0 (*n* = 12)
UFOV Divided Attention	110.3 ± 166.2 (*n* = 9)	24.1 ± 1.5 (*n* = 8)	24.7 ± 2.6 (*n* = 7)	36.9 ± 32.4 (*n* = 13)	43.0 ± 60.0 (*n* = 11)	25.6 ± 5.0 (*n* = 10)	58.0 ± 78.2 (*n* = 15)	24.3 ± 2.5 (*n* = 13)	34.7 ± 39.4 (*n* = 12)
UFOV Selective Attention	190.3 ± 132.2 (*n* = 9)	103.7 ± 30.5 (*n* = 8)	95.6 ± 38.0 (*n* = 7)	123.7 ± 68.7 (*n* = 13)	119.0 ± 100.8 (*n* = 11)	115.6 ± 81.3 (*n* = 10)	129.9 ± 117.9 (*n* = 15)	99.5 ± 44.7 (*n* = 13)	94.7 ± 78.3 (*n* = 12)
Computer-Based Tasks									
Singleton d'	−0.145 ± 0.090 (*n* = 9)	−0.033 ± 0.128 (*n* = 8)	−0.061 ± 0.138 (*n* = 8)	−0.011 ± 0.123 (*n* = 14)	0.005 ± 0.132 (*n* = 11)	0.060 ± 0.166 (*n* = 10)	−0.104 ± 0.150 (*n* = 15)	0.026 ± 0.182 (*n* = 12)	−0.002 ± 0.156 (*n* = 11)
Contingent d'	0.083 ± 0.130 (*n* = 9)	0.222 ± 0.231 (*n* = 8)	0.152 ± 0.175 (*n* = 8)	0.221 ± 0.187 (*n* = 14)	0.194 ± 0.151 (*n* = 11)	0.257 ± 0.218 (*n* = 10)	0.223 ± 0.157 (*n* = 15)	0.269 ± 0.219 (*n* = 12)	0.176 ± 0.164 (*n* = 11)

(*continued on next page*)

Table 2 (*continued*)

	CTX +			CTX −			HC		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
Load Effect	0.16 ± 0.06 (*n* = 9)	0.11 ± 0.04 (*n* = 8)	0.14 ± 0.08 (*n* = 8)	0.15 ± 0.05 (*n* = 13)	0.16 ± 0.05 (*n* = 11)	0.15 ± 0.06 (*n* = 10)	0.12 ± 0.07 (*n* = 14)	0.12 ± 0.07 (*n* = 11)	0.11 ± 0.10 (*n* = 11)
Filter Effect	0.001 ± 0.02 (*n* = 9)	−0.012 ± 0.036 (*n* = 8)	0.007 ± 0.021 (*n* = 8)	0.003 ± 0.020 (*n* = 13)	0.014 ± 0.028 (*n* = 11)	−0.005 ± 0.017 (*n* = 10)	0.006 ± 0.020 (*n* = 14)	0.005 ± 0.025 (*n* = 11)	−0.001 ± 0.021 (*n* = 11)
ERPs									
N2pc Low-Similarity	−0.504 ± 0.396 (*n* = 8)	−0.308 ± 0.653 (*n* = 8)	−0.266 ± 0.661 (*n* = 8)	−0.407 ± 0.877 (*n* = 14)	−0.494 ± 0.961 (*n* = 10)	−0.643 ± 0.488 (*n* = 10)	0.075 ± 0.284 (*n* = 15)	−0.412 ± 0.701 (*n* = 11)	0.610 ± 0.935 (*n* = 11)
N2pc High-Similarity	−1.00 ± 0.645 (*n* = 8)	−0.634 ± 0.567 (*n* = 8)	−0.653 ± 1.018 (*n* = 8)	−0.878 ± 1.008 (*n* = 14)	−1.051 ± 0.960 (*n* = 10)	−0.668 ± 1.352 (*n* = 10)	−0.446 ± 0.490 (*n* = 15)	−0.812 ± 0.824 (*n* = 11)	−1.160 ± 0.857 (*n* = 11)
CDA Load Effect	−0.761 ± 0.803 (*n* = 8)	−0.701 ± 0.576 (*n* = 8)	−0.838 ± 0.655 (*n* = 8)	−0.729 ± 0.765 (*n* = 12)	−0.897 ± 0.765 (*n* = 10)	−0.324 ± 0.626 (*n* = 9)	−0.709 ± 0.778 (*n* = 14)	−0.530 ± 0.629 (*n* = 11)	−0.903 ± 0.893 (*n* = 10)
CDA Filter Effect	−0.348 ± 0.208 (*n* = 8)	0.022 ± 0.415 (*n* = 8)	−0.553 ± 0.513 (*n* = 8)	−0.214 ± 0.636 (*n* = 12)	−0.434 ± 0.365 (*n* = 10)	−0.234 ± 0.356 (*n* = 9)	−0.060 ± 0.472 (*n* = 14)	−0.102 ± 0.297 (*n* = 11)	−0.248 ± 0.631 (*n* = 10)

(Ctx + = Chemotherapy patient group; Ctx − = non-chemotherapy patient group; HC = healthy control group; OD = right eye; OS = left eye; RNFL = retinal nerve fiber layer; GCL = ganglion cell layer; -W = word; -C = color; -CW = color-word; -I = interference; PASAT = paced auditory serial attention task; UFOV = useful field of view; CDA = contralateral delay activity).

measurements at least three months after completing chemotherapy, whereas our measurements were taken during initial chemotherapy cycles. Together, these preliminary results suggest chemotherapy-related impairments in visual function is at least partially associated with changes in retinal structure.

Future studies will benefit from considering the contribution of visual pathway degeneration to CRCI [40,41]. Information processing models assume sensory organs must process information first before cognitive functions may act on them. Despite this assumption, most CRCI studies have incorporated measures of visual cognition without considering contributions from the retina. Ophthalmic measures allow for the dissociation between retinal and cognitive dysfunction in cancer patients receiving chemotherapy, which may reveal either: (1) patterns of retinal and cognitive dysfunction may be unrelated, which would suggest independent mechanisms contribute to changes in retinal and cognitive function; or (2) patterns of retinal dysfunction may predict patterns of cognitive dysfunction, which would suggest a common mechanism contributes to changes in retinal and cognitive function. Disentangling retinal and cognitive dysfunction may yield important insights into the underlying mechanisms of chemotherapy-related neurotoxicity [41].

Recent evidence suggests mechanisms of visual pathway degeneration and CRCI may overlap. Pergolizzi and colleagues [42] measured visual memory task-evoked functional magnetic resonance imaging (fMRI) activity in breast cancer patients before and after receiving chemotherapy. Patients, relative to healthy comparisons measured at similar intervals, showed chemotherapy-related reductions in task-evoked fMRI activity in posterior brain regions within the ventral visual processing stream [43]. Although no change in visual memory task performance was observed, breast cancer patients showed a chemotherapy-related increase in task-evoked fMRI activity in frontal brain regions. Similar patterns of results have been reported in the cognitive aging literature [44–46]. According to the compensatory aging hypothesis [47,48], compensatory mechanisms overcome degeneration of posterior brain regions via overactivation of frontal brain regions, often leading to no apparent difference in task performance. Similarities between empirical patterns reported in CRCI and cognitive aging literatures have led to the hypothesis that chemotherapy accelerates the aging process [2,49]. Whether chemotherapy-related visual pathway degeneration results from similar aging mechanisms remains an unanswered question.

There are several potential limitations to be considered. First, we examined a relatively small sample size with incomplete follow-up, thus limiting the power of this feasibility study. Our results are intended to be primarily descriptive, providing the first examination of chemotherapy-related changes in ophthalmic and neurophysiologic markers in hematologic cancer patients. Future large-scale studies are necessary to confirm preliminary findings, including trending and non-significant results with moderate effect sizes, reported here. Second, we studied a patient sample comprised of heterogeneous cancer diagnoses and chemotherapy protocols. We were therefore unable to determine the disease- or treatment-specificity of our findings. Finally, this feasibility study evaluated acute changes in ophthalmic and neurophysiologic measures following initial chemotherapy administration in hematologic cancer patients; it remains to be determined how our findings relate to long-term hematologic cancer survivors.

In conclusion, our feasibility study showed that combining neurophysiologic and ophthalmic markers can provide novel insights into CRCI. Further work is needed to confirm preliminary findings reported here, and to extend them to other cancer populations and treatment protocols. By performing comparative studies of retinal and cortical degeneration in cancer patients, future clinical studies may be able to use rapid and non-invasive ophthalmic markers to track onset and progression of chemotherapy-related neurotoxicity and cognitive impairment.

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Declaration of Competing Interest

Sachin Kedar has a licensed technology for Advanced Pupil Simulator with EON Reality Inc. All other authors declare there is no conflict of interest regarding the publication of this work.

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