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A Hypothesis-Generating Study Using Electrophysiology to Examine Cognitive Function in Colon Cancer Patients

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Abstract

Introduction: The purpose of this study was to describe the trajectory of cognitive function using neuropsychological tests and electrophysiological measures in individuals receiving 5FU/oxaliplatin chemotherapy for colon cancer.
Methods: A total of 10 participants were tested at baseline (within 3 weeks of starting chemotherapy), 6 months (coinciding with the end of chemotherapy treatment), and 12 months (approximately 6 months post-chemotherapy). Participants completed neuropsychological tests and electrophysiology recordings of P300 event-related potential (ERP) elicited by a sustained attention to response task paired with experience sampling of attentional states (subjective reports of on-task or mind wandering).
Results: No change in mean neuropsychological test performance was observed. Comparison of mean P300 ERP amplitudes as a function of attentional states (on-task vs. mind wandering) revealed no main effect of attentional state observed at baseline or 6 months, but a significant effect of attention was observed at 12 months, consistent with effects observed in healthy individuals.
Conclusions: Future studies can consider sustained attention constructs when studying cognitive function in colon cancer patients.

Keywords: Electrophysiological studies; Neurotoxicity; Attention; Colon cancer; Cognition; Chemotherapy; Mind wandering; Sustained attention

Introduction

Cognitive impairment following chemotherapy treatment has been reported in 17%–78% of cancer patients (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005). The chemotherapy regime of 5-fluorouracil and oxaliplatin (FOLFOX), commonly used to treat colon cancer, is neurotoxic and potentially associated with cognitive impairment (Hildebrand, 2008). Studies to date report mixed patterns of longitudinal changes in cognition among colon cancer patients receiving chemotherapy using neuropsychological tests (Andreis et al., 2013; Cruzado et al., 2014; Vardy et al., 2015).

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Assessing cancer-related cognitive impairment is challenging. The International Cognition and Cancer Task Force (ICCTF) recommends selected neuropsychological tests that characterize learning and memory, processing speed, and executive function (Wefel, Vardy, Ahles, & Schagen, 2011). Although these cognitive domains were described as most effected in cancer patients (Jansen et al., 2005), a scoping review emphasized the importance of assessing the remaining cognitive domains, including attention (Olson et al., 2016). Furthermore, although neuropsychological tests are considered gold standard for assessing cognition for various pathologies, other methodologies may further our understanding of cancer-related cognitive impairment.

Mind wandering is an attention-based construct describing periods of time in normal, daily living when thoughts are decoupled from the ongoing task at hand (Handy & Kam, 2015). Mind wandering is related to functional brain networks associated with attention, as shown in electroencephalography (EEG) studies (Kirschner, Kam, Handy, & Ward, 2012). One study previously investigated mind wandering in breast cancer patients post-chemotherapy, and reported abnormal patterns of sustained attention compared with healthy controls using EEG during a sustained attention to response task (SART; Kam et al., 2016).

Attention was impaired in a large cohort of colorectal cancer patients (Vardy et al., 2015). No known studies have used EEG during SART paired with experience sampling of attentional state (i.e., subjective reports of being on-task or mind wandering) to characterize cognitive changes in colon cancer patients treated with chemotherapy. As a hypothesis-generating study to explore mind wandering in colon cancer patients, we described longitudinal changes in cognitive function in colon cancer patients undergoing FOLFOX chemotherapy using a battery of neuropsychological tests and EEG during SART.

Materials and Methods

Study Recruitment and Protocol

Ethical approval was obtained from the British Columbia Cancer (BC Cancer) Research Ethics Board (H10-00803). Participants were recruited via referral from the BC Cancer-Vancouver medical oncologists from September 2012 to January 2015. All participants provided informed consent prior to baseline testing. Study inclusion criteria were adults $\geq$19 years; scheduled to receive FOLFOX adjuvant chemotherapy treatment for colon cancer; and adequate understanding of English. Participants were excluded if they scored $<$23 on the Mini Mental State Examination, had pre-existing health conditions or medications influencing cognition, and a history of substance abuse or diagnosed neurological disorders.

The longitudinal study included three timepoints: baseline (before or within 3 weeks of starting chemotherapy treatment), 6 months (coinciding with the end of chemotherapy treatment), and 12 months (6 months post-chemotherapy treatment completion). Each session included a neuropsychological test battery, self-report questionnaires, and SART with EEG recordings. The neuropsychological test battery was completed in a single session in a quiet laboratory at the University of British Columbia (UBC) by a single, trained study team member. The order of individual neuropsychological tests was consistent across all study sessions. EEG testing was conducted in an electrophysiology laboratory at UBC by a trained study team member. Neuropsychological testing and EEG testing sessions were scheduled at various times of day depending on participant availability. In total, each study session was approximately 4 hr.

Study Outcomes

Participant demographics and medical information. Self-reported participant age, highest level of education, marital status, and current employment were collected. Participant height and weight were measured at each study session, and body mass index was calculated. Total oxaliplatin chemotherapy treatment dose, other cancer treatments (i.e., surgery), and cancer stage were extracted from medical records supervised by a study medical oncologist (H.J. Lim).

Self-report questionnaires. Self-reported cognitive function was assessed using the Functional Assessment of Cancer Therapy (FACT) Cognitive Function (FACT-Cog; Wagner, Sweet, Butt, & Cella, 2009). Other questionnaires included the 10-Item Centre for Epidemiologic Studies Depression Scale (Andresen, Malmgren, Carter, & Patrick, 1994), FACT-Fatigue (FACT-F; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997), and 10-Item State-Trait Anxiety Inventory (Marteau & Bekker, 1992). Usual physical activity was assessed using the International Physical Activity Questionnaire–Long Version (Craig et al., 2003).

Neuropsychological test battery. The selection of neuropsychological tests was informed by the ICCTF recommendations (Wefel et al., 2011), including the Hopkins Verbal Learning Test-Revised (HVLT-R) for learning and memory, Trail Making Test A&B for processing speed and executive function, and Controlled Oral Word Association Test (COWA; FAS letterset) and animal naming for verbal fluency and executive function. These neuropsychological tests were administered by paper and pencil.

The Stroop Test was used to assess executive functioning and was administered by computer. The difference in response time (RT) between the neutral (non-color words printed in red, blue, or green) and incongruent (word color does not match the name) trials is the primary measure and represents the Stroop semantic interference effect (the meaning of the word causes interference; Bench et al., 1993). Smaller differences in RT represent better response inhibition to the meaning of the word while responding to the color. Further Stroop Test methodological details are found in online Supplementary Data I.

SART. Participants performed a visual SART while their EEG was recorded. Specifically, a serial stream of single letters and digits was viewed, with participants responding to frequent targets (digits) and withholding responses to infrequent nontargets (letters; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). At the end of each trial block participants verbally reported their attentional state ("on-task" vs. "mind wandering") based on descriptions given at the start of testing; block lengths were randomly varied from 30 s to 90 s (or 15–45 trials) to maximize attentional variability and reduce predictability of attentional reporting (Kam et al., 2011); up to 40 blocks were completed by each participant. EEG was recorded from 64 active scalp electrodes, along with vertical and horizontal electrooculograms and electrodes on each mastoid. EEG data were analyzed using ERPLAB toolbox (https://erpinfo.org/erplab/). The ERP analyses reported below were based on mean amplitude measures taken relative to a –200 to 0 ms pre-stimulus baseline. To compare ERP responses between on-task and mind wandering states, we only included the six targets in our ERP averages that were presented in the 12 s preceding each attentional report (on-task vs. mind wandering)—a time window that maximizes the number of events that can be included in the ERP averages while still maintaining a reasonable fidelity to the actual attentional report (Kam et al., 2011, 2016). Four participants were excluded in the 12-month timepoint analysis—one due to participant drop out, two due to equipment technical difficulties during testing, and one due to data file corruption during data extraction. Complete SART and EEG methodological details are found in online Supplementary Data I.

Statistical Analysis

Participant demographics and clinical characteristics are summarized as means, standard deviations (SD), or categorically summed in tables. Neuropsychological test performance, self-report questionnaire, SART behavior, and P300 ERP amplitudes are summarized as means and SD in tables. Group-averaged ERP waveforms are shown graphically. Statistical analysis was conducted using IBM SPSS Statistics, version 22.0 (IBM Corporation, Armonk, NY) with accepted levels of significance at $p < 0.05$. Friedman Test and post hoc Wilcoxon Signed-Rank Test with Bonferroni Correction ($p < 0.017$) were used to assess change in neuropsychological and self-report questionnaire outcomes across timepoints. Repeated measures analysis of variance (ANOVA) was conducted to examine differences in attentional state reporting and behavioral performance (accuracy and false alarm rate) across timepoints and mean amplitudes of task-induced P300 ERPs between attentional states (on-task or mind wandering) within each timepoint. Post hoc repeated measures ANOVA was conducted to examine the interaction of attention state and timepoints and the main effect on attention state on P300 ERPs.

Results

Participants

A total of 18 patients were screened; 8 were not tested (6 not interested, 1 difficulty scheduling, and 1 refused chemotherapy treatment). A total of 10 participants were recruited (mean age 51.7 years; 50% female), and their characteristics are summarized on Table 1. One participant did not complete the 12-month study outcomes due to work commitments. One participant's 12-month self-report questionnaire outcomes were incomplete and excluded from the analysis. Another participant's 12-month FACT-F and FACT-Cog outcomes were partially completed and excluded from the analysis.

Neuropsychological and Questionnaire Outcomes

The neuropsychological test battery and self-report questionnaire results are summarized in Table 2. Significant differences were observed for the FACT-G social well-being subscale ($\chi^2 = 8.22$, df = 2, $p = 0.02$). Post hoc analysis did not detect differences in FACT-G social well-being from baseline to 6 months ($Z = -1.13$, df = 2, $p = 0.26$) or 6 months to 12 months ($Z = -0.52$, df = 2, $p = 0.61$), but detected a significant decrease from baseline to 12 months ($Z = -2.40$, df = 2, $p = 0.016$). Near significant differences were observed for HVLT-R Retention scores ($\chi^2 = 5.87$, df = 2, $p = 0.05$), FACT-G physical well-being subscale ($\chi^2 = 5.87$, df = 2, $p = 0.05$), COWA Test ($\chi^2 = 5.56$, df = 2, $p = 0.06$), and incongruent RT for the Stroop Test ($\chi^2 = 5.25$, df = 2,

Table 1. Participant demographic and clinical characteristics

Participant characteristics	Mean (SD) or number (%)
Age at recruitment (years)	51.7 (7.3)
Sex (female)	5 (50%)
Body mass index (kilogram/metre^2)	24.9 (3.1)
Education	
High school diploma	1 (10%)
Post-secondary training (vocational, college or bachelor degrees)	5 (50%)
Post-graduate degrees (professional training, master's or doctoral degrees)	4 (40%)
Marital status	
Currently married	8 (80%)
Never married	2 (20%)
Employment status	
Full-time	5 (50%)
Part-time	1 (10%)
On leave from work	4 (40%)
Place of birth	
Canada	7 (70%)
China	2 (20%)
Russia	1 (10%)
Cancer stage	
1	0 (0%)
2	1 (10%)
3	9 (90%)
Cancer treatments	
Oxaliplatin chemotherapy dose (milligrams)	1,396.6 (395.4)
Received surgery	10 (100%)

$p = 0.07$). However, post hoc analysis detected no differences between timepoints (data not shown). A nonsignificant reduction in mean Interference Effect from the Stroop Test was observed from baseline, 6 months, and 12 months (138 ms, 100 ms, and 72 ms, respectively; $\chi^2 = 4.75$, df = 2, $p = 0.09$).

Electrophysiological Testing

SART behavior and electrophysiology results are summarized in Table 2.

Behavior. The hit rate for targets was 98% at baseline, 93% at 6 months, and 95% at 12 months. The false alarm rate for the nontargets was 25% at baseline, 27% at 6 months, and 25% at 12 months. Finally, the mean frequency of mind wandering reports was 44% at baseline, 46% at 6 months, and 44% at 12 months. No significant difference in hit rate, false alarm rate, and mind wandering frequency were observed.

Electrophysiology. For each study timepoint, the group-averaged P300 ERP component elicited by target events during the SART is shown in Fig. 1 (available as Supplementary Data at *Archives of Clinical Neuropsychology* online) at midline central or posterior scalp electrode sites Cz, CPz, and Pz, as a function of attentional report (on-task or mind wandering); mean amplitudes for analyses were measured across a 375–575 ms post-stimulus time window, as highlighted in the figure. There was no main effect of attentional state on P300 amplitude at baseline [$F(1,9) = 2.83$, $p = 0.13$] or at 6 months [$F(1,9) = 2.53$, $p = 0.15$]. At 12 months there was a main effect, where the amplitude of the P300 elicited by target events was significantly greater for targets presented in the time interval immediately preceding an on-task versus mind wandering attentional report [$F(1,5) = 7.57$, $p = 0.04$]. Taken together, this suggests that whereas the amplitude of the P300 did not vary with attentional state at baseline and 6 months, by 12 months the P300 amplitude was significantly larger when attention was reported as on-task relative to mind wandering. To examine this possibility more directly, we conducted a post hoc repeated measures ANOVA on the ERP data from the six participants who completed EEG testing across all three timepoints; an interaction between attentional report and timepoint approached but did not meet significance [$F(2,4) = 5.26$, $p = 0.08$].

Table 2. Summary of means (SD) for neuropsychological test battery, self-report questionnaires, and SART outcomes

	Baseline (n = 10)	6 months (n = 10)	12 months(n = 9)	χ^{2} [c]	p-value
Neuropsychological test battery outcomes					
Stroop Test					
Congruent RT (ms)	800 (153)	744 (128)	737 (143)	2.25	0.33
Congruent accuracy (%)	98.7 (2.5)	99.3 (1.2)	98.8 (2.3)	0.62	0.74
Incongruent RT (ms)	951 (220)	866 (159)	836 (154)	5.25	0.07
Incongruent accuracy (%)	98.1 (1.6)	98.0 (2.6)	98.8 (2.3)	1.75	0.42
Neutral RT (ms)	813 (156)	766 (120)	764 (151)	1.00	0.61
Neutral accuracy (%)	99.8 (0.5)	98.5 (1.8)	99.2 (1.8)	1.08	0.58
Interference effect (ms)	138 (93)	100 (74)	72 (32)	4.75	0.09
Hopkins Verbal Learning Test—Revised					
Total recall	45.8 (10.1)	47.4 (13.0)	48.2 (11.7)	0.79	0.67
Delayed recall	45.0 (14.4)	45.7 (12.9)	49.9 (9.1)	1.93	0.38
Retention	45.6 (15.0)	45.1 (6.9)	52.0 (7.1)	5.87	0.05
RDI	46.8 (9.0)	46.0 (12.5)	50.7 (5.6)	0.94	0.63
COWA Test	37.2 (9.7)	42.7 (8.7)	39.3 (10.0)	5.56	0.06
Animal naming	16.5 (4.0)	16.2 (4.2)	18.0 (4.3)	2.97	0.23
Trails A (s)	27.2 (6.0)	29.7 (10.5)	27.7 (8.8)	2.00	0.37
Trails B (s)	63.2 (15.2)	65.9 (23.6)	63.8 (22.3)	0.40	0.82
Self-report cognitive impairments					
FACT—Cog[b]					
Perceived cognitive impairment	61.2 (11.1)	54.5 (15.3)	60.2 (11.8)	3.71	0.16
Impact on quality of life	11.8 (5.4)	11.9 (4.6)	14.6 (1.8)	2.67	0.26
Comments of others	15.5 (1.6)	14.8 (1.8)	15.0 (1.5)	2.71	0.26
Perceived cognitive abilities	21.4 (7.1)	18.4 (7.0)	24.0 (4.5)	3.22	0.20
Other self-report questionnaires					
Usual physical activity (IPAQ; MET-h/wk)[a]	11.6 (12.0)	16.6 (10.7)	15.3 (13.2)	4.20	0.12
Depression (CES-D)[a]	14.6 (2.0)	14.3 (2.4)	14.5 (2.5)	1.31	0.52
Anxiety (STAI)[a]	21.8 (4.1)	18.6 (3.4)	21.0 (2.9)	4.20	0.12
Fatigue (FACT-F TOI)[b]	76.1 (23.7)	76.7 (21.1)	90.9 (11.4)	4.52	0.10
Well-being (FACT-G)[b]					
Physical well-being	20.4 (7.6)	20.6 (5.0)	25.6 (1.5)	5.87	0.05
Social well-being	23.7 (3.7)	23.2 (3.0)	21.8 (4.3)	8.22	0.02
Emotional well-being	20.3 (1.9)	20.2 (2.0)	20.3 (2.1)	0.93	0.63
Functional well-being	36.9 (13.5)	35.8 (12.7)	44.1 (5.2)	2.60	0.27
SART					
Behavior					
Hit rates (%)	98 (1)	93 (13)	95 (6)	0.67[d]	0.67
False alarm rates (%)	25 (7)	27 (12)	25 (14)	0.23[d]	0.80
Mind wandering frequency (%)	44 (15)	46 (15)	44 (16)	0.024[d]	0.98
Electrophysiology—Mean P300 ERP Amplitudes (μV)					
Electrode Cz					
On-task	2.40 (3.20)	2.13 (2.81)	3.71 (4.69)		
Mind wandering	0.79 (2.72)	1.65 (2.00)	2.74 (2.84)		
Electrode CPz					
On-task	2.87 (2.72)	2.40 (2.02)	5.04 (3.13)		
Mind wandering	1.49 (2.32)	1.83 (1.54)	2.60 (0.98)		
Electrode Pz					
On-task	2.56 (2.33)	1.90 (1.83)	2.12 (1.46)		
Mind wandering	1.39 (2.04)	1.29 (2.05)	1.72 (1.32)		

RT, response time; ms, milliseconds; RDI, Recognition Discrimination Index; COWA, Controlled Oral Word Association; IPAQ, International Physical Activity Questionnaire Long Version; MET-h/wk, metabolic equivalent-hour/week; CES-D, 10-Item Centre for Epidemiologic Studies Depression Scale; STAI, 10-Item State Trait Anxiety Inventory; FACT–F, Functional Assessment of Cancer Therapy–Fatigue; TOI, Trials Outcome Index; FACT–G, Functional Assessment of Cancer Therapy–General; FACT–Cog, Functional Assessment of Cancer Therapy–Cognitive; ERP, event-related potentials; μV, microvolts.

[a] n = 8 included in analysis at 12-month timepoint.
[b] n = 7 included in analysis at 12-month timepoint.
[c] Degrees of freedom (df) = 2.
[d] Repeated measures ANOVA; F-statistics *(2, 12).*

Discussion

In this hypothesis-generating study assessing longitudinal changes in colon cancer patients treated with the standard 6 months regime of FOLFOX chemotherapy, no significant change in self-reported cognitive function or neuropsychological tests battery performance was observed. Our findings are consistent with Andreis and colleagues (2013) who reported no change in cognition using similar neuropsychological tests and longitudinal design in 57 consecutive colorectal cancer patients receiving FOLFOX chemotherapy.

However, we did find evidence suggesting a longitudinal change in attentional function, as assessed via ERP-based measures of target processing in the context of a SART paradigm. Specifically in healthy young adults, the amplitude of the P300 ERP component elicited by visual targets in the SART is systematically larger during on-task versus mind wandering attentional states (Kam et al., 2011; Smallwood, Beach, Schooler, & Handy, 2008), a finding consistent with reduced neurocognitive engagement from ongoing events in the external environment during periods of mind wandering (Handy & Kam, 2015; Kam & Handy, 2013). While participants in the current study showed this same normative increase in P300 amplitude during on-task attentional states at the 12-month timepoint (6 months post-chemotherapy treatment), P300 amplitudes remained unaffected by attentional state at baseline and 6-month study timepoints (post-chemotherapy treatment). This finding supports two central points.

First, it suggests that while colon cancer patients before and immediately after FOLFOX chemotherapy treatment may have reduced neurocognitive engagement with the external task environment even when they subjectively report being "on-task", this pattern of altered attentional capacity may have normalized 6 months after chemotherapy treatment. Second, using the same SART paradigm and ERP measures in a population of breast cancer survivors with self-reported complaints of "chemo-brain", similar nonnormative patterns were found—while the P300 amplitude elicited by target events was attenuated by self-reported attentional state within breast cancer patients, their on-task P300 amplitudes were comparable to those recorded during periods of mind wandering in cognitively healthy age-matched controls (Kam et al., 2016). Building on this, the current study found significant ERP effects of attentional states at the 12-month timepoint in the absence of clear changes in SART behavioral performance, the frequency of self-reported attentional states, and performance in neuropsychological tests. This highlights the potential utility of using ERP measures and experience sampling in cancer patients to examine attentional engagement and neurocognitive processes not identifiable by behavioral cognitive outcomes alone. The observed changes in attentional engagement during the SART paradigm may be paralleled by performance in the Stroop Test. Larger interference effects may be in part due to failure of selective attention during a response conflict (Bench et al., 1993). Although not statistically different, we observed a relatively stable mean interference effect at baseline and 6-month study timepoints (138 ms and 100 ms, respectively) and a reduction at 12 months, suggesting improvement (72 ms). However, the lack of a comparison healthy control group and a small sample size limits this study's ability to make robust conclusions.

The lack of observed change in neuropsychological tests performance may be explained by several reasons. Firstly, although the neuropsychological tests were recommended by the ICCTF to harmonize cognitive assessment approaches in cancer patients (Wefel et al., 2011) and are validated for clinical use in other populations (i.e., dementia), cognitive changes in non-central nervous system cancer patients may follow different patterns and may not be as salient as people with neurological disorders (Olson et al., 2016). Secondly, this study did not aim to specifically recruit and phenotype only those who complained of cognitive changes after a colon cancer diagnosis. Cognitive changes in colon cancer patients is likely heterogenous in presentation and incidence, as described in up to 43% at diagnosis and up to 46% at 12-month follow-up with no added effect due to chemotherapy (Vardy et al., 2015). Selective recruitment may be challenging because appropriate screening tools for cognitive impairment in colon cancer patient are not yet determined.

This study has several limitations. First, as a hypothesis-generating study, the small study sample limits the statistical power for covariate analysis and robust conclusions. Second, this study recruited individuals receiving FOLFOX chemotherapy, and cognitive impairments may occur within a broader colon cancer population (Vardy et al., 2015). Thirdly, participant ethnicity data were not collected, which may limit interpretability of study findings. Finally, without a healthy control comparison group, it was difficult to compare neuropsychological performance and EEG measurements with normative data.

Conclusion

Using a longitudinal study design, no significant changes in neuropsychological test battery performance were observed. However, this hypothesis-generating study described changes in patterns of neurocognitive engagement using electrophysiological measures during a sustained attention task. These results suggest potential utility in EEG measures during SART and sustained attention constructs to study cognitive function in individuals diagnosed with colon cancer with larger sample sizes.

Supplementary Data

Supplementary material is available at *Archives of Clinical Neuropsychology* online.

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Conflict of Interest

None declared.

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