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ELECTROPHYSIOLOGICAL BIOMARKERS OF CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENT IN HEMATOLOGICAL MALIGNANCY PATIENTS

by

David Eugene Anderson

A DISSERTATION

Presented to the Faculty of
the University of Nebraska Graduate College
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

Medical Sciences Interdepartmental Area
Graduate Program
(Internal Medicine)

Under the Supervision of Professor Matthew Rizzo

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ABSTRACT

Electrophysiological biomarkers of chemotherapy-related cognitive impairment in hematological malignancy

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University of Nebraska, 2018

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Multiple cancer populations frequently report cognitive impairment following treatment with chemotherapy agents ("chemo-brain"). Impaired neuropsychological performance is commonly reported in cognitive domains of attention and executive function. Understanding neural mechanisms underlying cognitive impairments is essential to developing prevention and rehabilitation strategies. Brain imaging studies frequently show chemotherapy-related impairments within the attentional control network, which is comprised of a constellation of cortical regions that govern reportedly impaired cognitive functions. In the current dissertation research, I developed a novel electrophysiology battery aimed at recording near-instantaneous neural activity within the attentional control network during cognitive task performance. Cancer patients diagnosed with hematological malignancy (e.g. lymphoma, myeloma) completed three longitudinal assessments: (1) prior to starting chemotherapy, and following (2) one-month and (3) three-months of chemotherapy. Comparison groups included patients not receiving chemotherapy and demographically-matched healthy controls. Outcome measures provide initial support for contributions from both tumor biology and chemotherapy toxicity to functional changes in attentional control network activity. Furthermore, both cancer groups showed evidence for reduced information processing capacity while completing a simulation of naturalistic driving behavior. These results provide a unique platform for understanding basic neural mechanisms and translational impacts of attentional control impairment in cancer patients. Future large-scale studies must be committed to confirming these results, and further innovative work is necessary to confirm the link between previous brain imaging studies and cognitive electrophysiology measures used here. Innovative chemotherapies are improving survivorship among cancer patients. Thus, ensuring long-term quality of life among our growing cancer survivor population is paramount to achieving the highest level of public health and safety.

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LIST OF ABBREVIATIONS

AMPA	a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
BR	bendamustine rituximab
BVRT	Benton visual retention test
BDNF	bone derived neurotrophic factor
COMT	catechol-O-methyltransferase
CEN	central executive network
CNS	central nervous system
Ctx+	chemotherapy treatment group
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CFT	complex figure test
CLTR	consistent long-term retrieval
CPT	continuous performance test
CDA	contralateral delay activity
COWA	controlled oral word association
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
DRS	dementia rating scale
DAN	dorsal attention network
DRG	dorsal root ganglion
EEG	electroencephalography

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ERP	event-related potential
EFN	executive function network
FEF	frontal eye fields
HC	healthy control group
HM	hematological malignancy
HSCT	hematopoietic stem cell transplant
HVLT	Hopkins verbal learning test
iAPF	individual alpha peak frequency
IFG	inferior frontal gyrus
IPL	inferior parietal lobule
IL-6	interleukin-6
IPS	intraparietal sulcus
LOG	lateral occipital gyrus
LSM	least-squared mean
MRI	magnetic resonance imaging
MEG	magnetoencephalography
MFG	medial frontal gyrus
MMSE	mini-mental state examination
MM	multiple myeloma
MDS	myelodysplastic syndrome
NMDA	N-methyl-D-aspartate
Ctx-	non-chemotherapy treatment group
NHL	non-Hodgkin lymphoma

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PASAT	paced auditory serial addition task
PET	Positron Emission Tomography
PTSD	post-traumatic stress disorder
PFC	prefrontal cortex
QoL	quality of life
RT	response time
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
N2pc	second negative potential in posterior contralateral electrode
5-HTTLPR	serotonin transporter-linked polymorphic region
SENSEI	Simulator for Ergonomics, Neuroscience, Safety Engineering & Innovation
SFG	superior frontal gyrus
SPL	superior parietal lobule
STG	superior temporal gyrus
STS	superior temporal sulcus
TMT	trail making test
TNF-α	tumor necrosis factor α
UFOV	useful field of view
VAN	ventral attention network
VFT	verbal fluency task
VSRT	visual skills for reading test
WCST	Wisconsin card sorting task

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INTRODUCTION

Cancer is a physically, emotionally, and mentally devastating disease that will be diagnosed in approximately 1.7 million people in the United States each year. Improvements in cancer diagnostics and treatments have improved 5-year relative survival from 48.7% in 1975 to 69.3% in 2009. Accordingly, the number of cancer survivors is expected to rise from an estimated 14.5 million in 2014 to 19 million by 2024. As cancer treatments continue to improve survival outcomes, long-term quality of life (QoL) is becoming a rapidly emerging public health concern among our growing cancer survivor population.

QoL is typically evaluated with self-assessed symptom severity and functional status inventories. In a recent survey of 604 cancer survivors and 6,166 non-cancer survivors,[1] symptom complaints were most prevalent in cancer survivors for pain (73.47%, OR=2.12), fatigue (68.58%, OR=1.4), sensory neuropathy (60.99%, OR=2.42), and cognitive dysfunction (32.22%, OR=1.78). Evaluating QoL using self-assessed inventories, however, requires the logical antecedent of having the capacity for being self-aware of dysfunctional states. In contrast to subjective self-assessment, gold-standard tools are available for measuring objective cognitive function. Current evidence suggests a weak relationship between subjective and objective functional assessments,[2–6] thus bringing into question the construct validity of self-assessments to evaluate functional status in cancer survivors. It is therefore critical to adequately characterize changes in functional status to ensure long-term QoL in cancer survivors.

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The goal of the current dissertation research was to better understand cancer- and chemotherapy-related cognitive impairment in hematological malignancies. In the following sections, I first provide a broad review of the epidemiology, pathology, and treatment of hematological malignancies. Next, I review the symptom burden and importance of symptom management for treatment outcomes in hematological malignancies. Next, I review patterns of cognitive impairment observed in hematological malignancies, and discuss them within the context of biological mechanisms emerging from human and animal research. Finally, I discuss the theoretical motivation and empirical goals of the current dissertation research.

Hematological Malignancies

Epidemiology, Pathology, and Treatment

Hematological malignancies are a broad class of blood cancers, including lymphoma, myelomas and leukemia. Epidemiological studies have reported that 1.29 million people in the United States have been diagnosed with a hematological malignancy, and will be diagnosed in an estimated 172,910 people in 2017.[7] Hematological malignancies account for 10.2% of total cancer cases and 9.7% of all cancer-related deaths, with 5-year survival approximated at 50%, 63%, and 73% for myeloma, leukemia, and lymphoma, respectively. [7]

Pathophysiology underlying hematological malignancies emerges from defects in the self-renewal and differentiation of normal hematopoietic stem cells[8]. Normal hematopoietic populations are regulated by self-renewal, differentiation, and apoptosis[9]. In contrast, aberrations in normal hematopoietic

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stem cells can lead to the production of leukemic stem cells that override apoptosis signaling, allowing malignant hematopoietic cells to survive indefinitely.

Hematological malignancies disrupt two major classes of hematopoietic cell lineages: myeloid and lymphoid. Myeloid cells play a major role in innate immunity and are involved in inflammatory cytokine secretion[10]. Malignancies of myeloid cells lead to myelodysplasic syndrome (MDS), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML). Lymphoid cells play a major role in both innate and adaptive immunity[11,12]. Malignancies of lymphoid cells lead to lymphomas, lymphocytic leukemias, including acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL), and myeloma.

Treatment for patients diagnosed with hematological malignancies typically involves either chemotherapy alone or in combination with hematopoietic stem cell transplant (HSCT). Chemotherapy is typically administered as a combination of antineoplastic drugs developed to selectively interfere with mechanisms of DNA synthesis[13–20], DNA repair[21–25], and immunosuppression[26–31] in malignant cells, leading to malignant cell death and suppression of the tumor microenvironment. If malignant tumors fail to respond to chemotherapy, patients may subsequently undergo a combination of high-dose chemotherapy and HSCT. Patients undergoing allogeneic HSCT receive donor stem cells following high-dose chemotherapy. Patients undergoing autologous HSCT, in contrast, have their own stem cells harvested prior to high-dose chemotherapy.

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Symptom Management and Outcomes

Effective symptom management is critical to long-term quality of life. Bryant and colleagues[32] developed a cancer survivor adaptation model, which assumes continuous cognitive appraisal of cancer survivor experiences leads to behavioral modifications that moderate disease- and treatment-related changes in quality of life. Factor analysis was used to determine how positive (e.g. empathy, health awareness, self-esteem) and negative (e.g. anxiety, depression, stress) behaviors influenced the relationship between clinical characteristics and quality of life, where quality of life was characterized by physical, social, emotional, and functional well-being. Quality of life was directly affected by age, income, and disease duration, as well as both positive and negative adaptation factors. Clinical characteristics indirectly affecting quality of life through both positive and negative adaptation were age, gender, race, and undergoing treatment. Clinical characteristics indirectly affecting quality of life through negative adaptation were education, received chemotherapy, comorbidity, psychosocial changes, disease duration, and social support. No clinical characteristics indirectly affected quality of life only through positive adaptation. Thus, negative, but not positive, behavioral adaptations are more likely to contribute to changes in quality of life, suggesting effective symptom management must prioritize management of negative behaviors.

Symptom management is also critical to cancer treatment outcomes. In a survival study of 90 older adults (65-89 years old) diagnosed with hematological malignancies[33], 63% of patients with baseline cognitive impairment survived to

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one-year follow-up evaluations compared to 88% of patients without baseline cognitive impairment. Hazard analyses revealed patients without baseline cognitive impairment were 3.3 times more likely to survive during the one-year interval. Physical activity has also been associated with improved overall survival[34–37]. These studies highlight the positive impact of physical and cognitive function on cancer survival. It is therefore critical to better understand how symptom management and functional status influences survival and long-term quality of life. For the remainder of this section, symptoms reported in hematological malignancies are reviewed.

Physical Function. Disease- and treatment-related changes have been shown in self-reported measures of physical function[38–45], including fatigue, exercise, and physical health. Physical health was impaired anywhere from 2 to 10 years after diagnosis[38,40,42,44,45], with frequency analyses showing impairments in up to 25% of reporting patients[38]. Greater changes in physical health were found in non-married patients, patients with more comorbidities, and patients reporting greater impairments in cognitive health[39]. Fatigue has been shown to be impaired anywhere from 3 months to 5 years after diagnosis.[40,41,44] Greater changes in fatigue were found in patients who were younger (<50 years), non-married, progressing in disease stage, reporting greater comorbidities, and reporting greater cognitive impairment[39,43]. Changes in physical function were not related to age, gender, race, or education[39]. Changes in physical function may be associated with results from other studies reporting up to 73% of patients

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engaging in none or some amount of exercise during treatment[38], though this relationship has not been directly shown.

Treatment-related changes in physical function have been mapped out in longitudinal studies of NHL and AML patients[33,46–48]. Prior to treatment, these studies found impaired physical function in NHL patients[47,48] and normal physical function in AML patients[46]. During treatment, NHL patients reported declines in physical function compared to baseline assessments[47,48], with low risk (according to the age-adjusted International Prognostic Index) patients showing greater decline relative to high risk patients[47]. Physical function was not assessed in AML patients during treatment in these studies. Both NHL and AML patients showed improvements to baseline levels of physical function, though NHL patients reported impaired physical function until 3-months post-treatment[46–48]. These studies suggest physical function in NHL patients is impaired prior to treatment, declines during treatment, and returns to (impaired) baseline levels 3-months following treatment.

Treatment-related changes in fatigue have been mapped out in longitudinal studies of AML, NHL, and MDS patients[33,46–49]. Prior to treatment, these studies demonstrated a high prevalence of self-reported fatigue across all patient groups[33,46–49], with rates of 100%[46], 65%[49], and 40%[33] in AML, AML/MDS, and broad patient groups, respectively. During treatment, 79% of AML/MDS patients reported clinically significant fatigue[49]; NHL patients reported significant increases in fatigue symptoms relative to baseline measurements[47,48], with low risk patients showing greater susceptibility to treatment-related increases in

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fatigue[47]. Following treatment, 85% of AML patients reported fatigue 12-months post-treatment[46]; fatigue symptoms returned to baseline levels as early as two weeks in NHL patients[47,48], with high risk NHL patients more likely to return to baseline levels than low risk NHL patients[47].

Emotional Function. Disease- and treatment-related factors have been associated with self-reported changes in emotional function[38–41,43,44]. Pathological changes in mood symptoms, such as depression and anxiety, are reported under the umbrella of emotional function. Changes in emotional function may emerge from either individual contributions from, or interactions between, the psychological impact of cancer diagnosis or biological impact of treatment[50,51]. Emotional function has been evaluated in hematological malignancy patients using a brief questionnaire that assesses general changes in mood[38,40,41,44], anxiety[38,39], or depression[38–40]. Following diagnosis, changes in mood, anxiety, or depression have been reported in up to 25%[38], 20%[38,39], and 16%[38,39], respectively. Anxiety symptoms have been associated with younger age, non-married marital status, and lower subjective cognitive function[39,43]. Depression symptoms have been associated with younger age, non-married marital status, disease progression, greater number of comorbidities, and lower subjective cognitive function[39]. Engaging in exercise-related activities has been associated with lower prevalence of anxiety and depression.[38] Studies failing to find changes in emotional function compared patients receiving chemotherapy to those not receiving chemotherapy[52,53], suggesting changes in emotional function are likely due to disease-related tumor burden or psychological trauma rather than

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treatment toxicity. More complex disease-related emotional traumas, such as post-traumatic stress disorder (PTSD), impose longer lasting emotional burden on patients. An estimated 39% of hematological malignancy patients reported PTSD symptoms up to 10-years post-diagnosis[54], where greater PTSD symptoms were observed in patients who were younger, non-white, less educated, made less than $30,000 annually, underwent stem cell transplant or biologic treatment, and still had active disease.

Treatment-related changes in emotional function have been mapped out in longitudinal studies of AML, CML, and NHL patients[33,46–48,55]. Prior to treatment, AML[46] and NHL[47,48] patients showed at least minor impairments in emotional function, with high risk NHL patients more likely to show impairment[47] and 16% of patients across multiple hematological malignancies showing impairment[33]. During treatment, emotional function of NHL patients either remained stable or improved[47] relative to baseline, whereas 33.3% of CML patients demonstrated treatment-related increases in depression symptoms relative to baseline[55]. Following treatment, emotional function of AML patients improved[46]; NHL patients remained stable at 14 days[48] and showed improvement after 3 months[47,48].

Cognitive Function. Higher-level mental functions, such as thinking, memory, and concentration, are critical skills that show well-documented disease- and treatment-related changes across multiple cancer types[56–59]. Outside of gold-standard neuropsychological testing, these functions are typically evaluated using self-assessment tools that ask patients to rate their own level of

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cognitive performance. Changes in mental functions have been demonstrated across multiple studies[39–45,53], with assessments occurring anywhere from 3-months[41] to 10-years[45] post-diagnosis. Approximately 32% of patients have reported impaired mental function compared to 7% of healthy controls[43]. Complaints of impaired mental function were most common in patients who were younger, non-married, and reported greater number of co-morbid conditions[39]. Scores on mental function assessments were correlated with physical health competence, mental health competence, anxiety, depression, and fatigue[39]. As discussed below, these tools are weakly related to objective measures of cognitive function, suggesting self-assessment of cognitive function may be more related to psychosocial factors than cognitive function per se.

Treatment-related changes in cognitive function have been mapped out in longitudinal studies of AML and NHL patients[46–48]. Prior to treatment, AML[46] and NHL[48] patients reported no cognitive symptoms, though high risk NHL patients were more likely to report cognitive symptoms than low risk NHL patients[48]. During treatment, NHL patients reported no changes in cognitive symptoms with respect to baseline reports[47,48]. Following treatment, AML[46] and NHL[47,48] patients reported no changes in cognitive symptoms with respect to baseline, suggesting these patients were unaware of any disease- or treatment-related changes in cognitive function.

Role Function. The goal of promoting effective symptom management is to ensure patients are returning to and maintaining their societal roles during and following treatment, thus minimizing disease- and treatment-related public health

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impact. Here, changes in role function are broadly defined as changes in activities of daily living, such as social function, employment, and independence. Importantly, these complex skills are attributable to physical, emotional, and cognitive functions described above. Changes in role functions have been noted in several studies[33,44,60–63], though most of these studies have focused on changes in employment[60–63]. In a series of studies, Horsboel and colleagues[61–63] examined changes in employment status in patients up to 9 months after being diagnosed with hematological malignancy. Patients were examined with respect to changes in sick leave[61], disability pension[62], and work subsidized employment[63]: (1) 54% of patients were on sick leave, with a prevalence of depressive symptoms reported in 40% of sick leave patients compared to 15% of working patients[61]; (2) 40% of patients were on disability pension, and relative risk assessments revealed myeloma and lymphoma patients were 22.1 and 5.1 times more likely, respectively, to be on disability pension compared to healthy controls[62]; (3) 17% of patients were on work subsidized employment, and relative risk assessments revealed myeloma and CML patients were 13.4 and 13.8 times more likely, respectively, to be on work subsidized employment compared to healthy controls[63]. In a separate study of NHL survivors surveyed 8-years post-diagnosis[60], approximately 70% of survivors were unemployed, and 41% of survivors indicated they had changed jobs, reduced the number of work hours, or stopped working entirely. Furthermore, working survivors reported better mental well-being than non-working survivors, and having received chemotherapy treatment was associated with lower psychological and social well-being.

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Treatment-related changes in role function have been mapped out in longitudinal studies of AML and NHL patients[46–48]. Prior to treatment, AML[46] and NHL[47,48] patients reported impairments in role function, with high risk NHL patients more likely to report role function impairments[47]. During treatment, NHL patients reported declines in role function relative to baseline measurements[47,48], and low risk patients were more likely to report declines in role function compared to high risk NHL patients[47]. Following treatment, AML patients remained impaired in role function[46], and NHL patients remained impaired after 14 days[48] then returned to baseline levels of role function after 3 months[47,48].

Treatment-related changes in social function have been mapped out in longitudinal studies of AML and NHL patients[46–48]. Prior to treatment, AML[46] and high-risk NHL[47] patients reported impairments in social function; in contrast, low-risk NHL[47] patients and an independent sample of NHL patients reported no impairments in social function[48]. During treatment, NHL patients reported no change in social function[47,48]. Following treatment, AML patients continued to experience impairments in social function and NHL patients experienced no difference in social function with respect to baseline function[46–48].

Treatment-related changes in activities of daily living have been mapped out in longitudinal studies of AML, MDS, and multiple hematological malignancies[33,49]. Prior to treatment, 37% of a heterogeneous sample[33] and 20% of MDS/AML[49] patients reported impairments in activities of daily living. During treatment, 21% of MDS/AML patients reported impairments in activities of daily

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living 1-month following treatment, though no significant difference was found with respect to baseline measurements.

Together, these studies indicate that better quality of life is a consequence of effective symptom management and contributes to overall societal impact. More work is necessary to elucidate symptom changes in patients across each hematological malignancy, and replication is necessary to confirm the pattern of symptoms reviewed above. Moving forward, however, more rigorous tools are needed to evaluate cancer-related symptoms. Specifically, these subjective measures are based solely on patient report. Critically, subjective and objective impairments are weakly related[2–6], suggesting patient reports may not reflect clinical standards for impairment. In the following section, objective clinical measures of cognitive function are evaluated.

Cognitive Impairment in Hematological Malignancies

Overview

Previous studies noting subjective changes in cognitive function are limited by the lack of knowledge regarding the construct validity in self-assessment tools[64]. Indeed, breast cancer studies have demonstrated weakly significant relationships between subjective cognitive function and objective cognitive performance[59], as determined by self-assessments and neurocognitive examinations, respectively. Neuropsychology testing instruments have been developed and validated to measure objective cognitive functions that are linked with known neurological disease and injury[65]. Thus, neuropsychology

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instruments are critical to understanding the nature and impact of cognitive impairment in hematological cancer patients.

Cross-sectional studies[40,43,52,53,66–69] have noted impaired objective cognitive performance across heterogeneous patient populations after either chemotherapy alone (Ctx+) or hematopoietic stem cell transplant (HSCT) following high-grade chemotherapy. Percentages of study samples demonstrating impaired cognitive performance ranges between 12%[67] and 75%[66], where up to 39% of patients showed impairment 9.5 years following treatment[53]. Due to the nature of cross-sectional study designs, it is difficult to determine whether disease- or treatment-related factors contribute to cognitive impairment. In contrast, longitudinal studies of patients prior to either Ctx+ or HSCT at least have baseline evaluations for comparison. For this reason, cross-sectional studies are not fully evaluated here. In the following sections, the impact of chemotherapy and HSCT are evaluated in turn to assess their respective contribution to cognitive impairment in hematological cancer patients.

Chemotherapy-Related Impairment

In a sample (n=68) of diffuse large B-cell non-Hodgkin lymphoma (DLBCL) patients[70], Khan and colleagues examined the effects of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (n=34) and R-CHOP (rituximab + CHOP) (n=34) on cognitive function using the Mini-Mental State Exam (MMSE)[71,72]. Cognitive function was evaluated prior to starting the first (TP0), second (TP1), third (TP2), and fourth (TP3) treatment cycles, where each treatment cycle lasted three weeks. Study patients were middle-aged adults

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(43.6±9.1 years), gender balanced (47.1% females), and were primarily diagnosed with stage II (43%) or III (41%) disease, though some stage IV patients (10%) were included. Patients in both treatment groups showed baseline impairments relative to normative data[72] and a significant decline in MMSE performance across treatment cycles. R-CHOP patients showed significant declines at TP2 and TP3 relative to TP0, whereas CHOP patients showed significant declines only at TP3 relative to TP0. Greater declines in MMSE performance in the R-CHOP group resulted in a significant difference between treatment groups at TP3. Thus, Khan and colleagues noted global cognitive impairment in DLBCL patients prior to treatment, and after 2 cycles (or 6 weeks) of R-CHOP and 3 cycles (or 9 weeks) of CHOP.

In a sample (n=30) of chronic myelogenous leukemia (CML) patients[55], Scheibel and colleagues examined the cognitive effects of interferon-alpha (IFN-α; n=13) alone or IFN-α and chemotherapy (low dose cytosine arabinoside or hydroxyurea; n=17). Cognitive function was assessed across multiple domains with six neuropsychology tests: Digit Symbol Substitution (psychomotor speed), CLTR (verbal learning), VSRT (verbal recall), Trails A (processing speed), Trails B (executive function), and COWA (verbal fluency). Assessments occurred prior to treatment and once during treatment. Study patients were middle-aged adults (46.5±9.6 years), mostly males (66.7%), and mid-treatment assessment occurred significantly later for the IFN-α and chemotherapy group (43.9±40.0 weeks) relative to the IFN-α alone group (22.9±24.0 weeks). Test performance was noted as impaired if it declined by at least one standard deviation. In total, 53.3%

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of patients showed a treatment-related decline on at least one test. Declines were noted most commonly in CLTR (20%), COWA (13.3%), and Trails B (26.7%). Depression symptoms increased in 33.3% of all patients, though no relationship was observed between changes in depressive symptoms and cognitive performance. Patients receiving IFN-α combination therapy showed greater declines in CLTR, COWA, and Trails B performance. Thus, Scheibel and colleagues demonstrated treatment-related impairments in verbal learning, verbal fluency, and executive function in CML patients following multiple treatment cycles.

In a sample (n=54) of acute myelogenous leukemia (AML; n=19) and myelodysplastic syndrome (MDS; n=35) patients[49], Meyers and colleagues examined cognitive effects of therapy with lipodaunocin and either cytoxan or topotecan, and some patients received an additional dose of thalidomide. Cognitive function was assessed seven neuropsychology tests: Digit Span (attention), Digit Symbol Substitution (psychomotor speed), HVLT (verbal memory), COWA (verbal fluency), Trails A (processing speed), Trails B (executive function), and Grooved Pegboard (motor dexterity). Assessment occurred prior to treatment (n=54) and one-month after initiating treatment in a subset of patients (n=26). Study patients were an average of 60.2 years old (21-84 years) and gender balanced (44% female). Test scores falling 1.5 standard deviations below normative data were noted as impaired. Prior to treatment, impairments were most commonly noted in HVLT (44%), Trails B (29%), Trails A (28%), and COWA (17%). Following one month of treatment, impairments were

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most commonly noted in HVLT (58%), Trails B (46%), Trails A (38%), and COWA (25%). Although more patients showed treatment-related impairments in these tests, the smaller sample at follow-up assessment reduced the power to detect these differences. Thus, Meyers and colleagues reported disease- and treatment-related impairment in AML and MDS patients in processing speed, executive function, verbal fluency, and verbal learning.

These studies, which represent the most rigorous evaluation of chemotherapy-related cognitive impairment in hematological cancer patients, are not without significant limitations. All three studies failed to include a non-treatment comparison group to rule out disease-related, in contrast to treatment-related, declines in cognitive function. According to current literature, impaired baseline cognitive function likely arose from putative disease-related systemic changes[50,73]. Furthermore, Khan and colleagues[70] measured cognitive function using the MMSE, a global cognitive screening tool designed to detect severe cognitive impairment, whereas cognitive changes reported in cancer patients are more consistent with mild cognitive impairment. Critically, the MMSE lacks sensitivity to detect mild cognitive impairment within specific cognitive domains[74,75]. Finally, Meyers and colleagues[49] studied a smaller subset of the initial sample during follow-up assessment, restricting the statistical power to detect reliable chemotherapy-related changes in cognitive function. Thus, more rigorous study designs and comprehensive neuropsychology batteries are required to evaluate evidence for and mechanisms of chemotherapy-related cognitive impairment in hematological cancer patients.

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Transplant-Related Impairment

In addition to standard chemotherapy, the toxicity of high-grade chemotherapy and HSCT poses an additional risk to cognitive function. Compared to the volume of chemotherapy-related cognitive impairment studies reviewed above, substantially more studies have investigated transplant-related cognitive impairment. In the following section, each study is grouped according to transplant type.

Allogeneic Transplant. Scherwath and colleagues[76] evaluated a study sample (n=102; 50.4±12.6 years; 67% males) comprised primarily of AML patients (41%) prior to (T0), 100±20 days after (T1), and 12±1 months (T2) after allogeneic HSCT. Cognitive function was examined in the domains of verbal working memory, visual working memory, verbal memory, reaction time, and fine motor function. No comparison groups were included, though performance was compared to normative data[65] and reliable change scores[77]. Prior to undergoing HSCT (T0), 47% of patients showed impairment in at least one domain, which may be explained by previous treatment with chemotherapy or autologous SCT in 80% of patients. Following HSCT (T2), 41% of patients showed impairment in at least one domain, and 72.6% of patients showed declines from T0 to T2. Older adults, lower education, and lower premorbid intelligence were associated with probability of cognitive impairment.

Schulz-Kinder and colleagues[78] examined a study sample (n=21; 41.7±12.4 years; 67.7% males) comprised primarily of AML patients (48%) prior to (T0) and 100±20 days after (T1) allogeneic SCT. Prior to SCT, 68.3% of

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patients received medium to strong induction chemotherapy. Cognitive function was examined in the domains of processing speed (Trails A), working memory (Digit Span, Visual Memory Span), verbal memory (VLMT), and executive function (Trails B, Go/NoGo). No comparison groups were included, though impairment was noted for test scores greater than 1.4 standard deviations below normative data [65]. Prior to (T0) and following (T1) HSCT, up to 26.3% and 42.1% of patients, respectively, showed cognitive impairment. There were no significant changes in cognitive function between T0 and T1 assessments.

Sostak and colleagues[79] examined a study sample (n=71; 37±9 years; 61% males) comprised primarily of AML (31%) and CML (45%) patients prior to (T0; 2±4 months) and 14 months after (T1) allogeneic HSCT. All CML and AML patients (and 96% of enrolled patients) had undergone induction chemotherapy prior to T0 assessment. In addition to neurological examination, cognitive function was examined in the domains of processing speed (Trails A, Digit Symbol Modalities) and executive function (Verbal Fluency Test, Stroop). No comparison groups were included, though test scores were considered impaired if they one standard deviation below the mean of normative data generated by the lab. Prior to HSCT, 62% and 58% of patients showed signs of abnormal neurological and neuropsychology status, respectively. Baseline neurological complications were primarily observed as tremors (38%) and impaired saccadic smooth pursuit (19%), and baseline neuropsychological impairments were observed primarily in the structured interview (36%), verbal fluency (24%), and Stroop interference scores (15%). At T1, 57% and 51% of patients showed

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neurological and neuropsychological complications, respectively. Compared to T0 status, 47% and 31% of patients showed new neurological and neuropsychological complications, respectively. Negative outcomes were associated with pre-SCT chemotherapy, transplant from an unrelated donor, and graft-versus-host disease (GvHD). Interestingly, 53% of patients with impaired neuropsychological performance at T0 showed improvement at T1, and gender (female) and disease duration (<20 months) were associated with positive outcomes.

Chang and colleagues[80] examined a study sample (n=106) of CML (86%; 45.2±11.9 years; 52% males) and MDS patients (14%; 64.8±9.3 years; 73% males). Patients underwent allogeneic HSCT (44%) or imatinib mesylate. Transplant patients completed assessments prior to (T0; 67±106 days), 12 months after (T1) and 18 months after (T2) allogeneic HSCT; other treatment patients completed assessments at the same intervals. Cognitive function was examined in the domains of processing speed (Trails A), executive function (Trails B, VFT), verbal learning and memory (Selective Reminding Task), and motor function (Grooved Pegboard). Cognitive performance was normalized to z-scores based on age, sex, and education per normative data[81–84]. Test performance was compared across transplant and non-transplant groups. Patients improved across testing intervals in measures of verbal learning and memory; no measures revealed a decline in cognitive performance. CML patients performed better than MDS patients in measures of motor control, processing speed, and executive function. Transplant patients performed worse than non-

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transplant patients in measures of motor control. These authors failed to report proportion of patients performing lower than normative data. Exclusion of a comparison group precluded evaluating changes in test performance relative to healthy controls. Thus, these data should be evaluated with caution, as improvements in test performance may reflect practice-related effects.

Meadows and colleagues[85] examined a study sample (n=77; 48.6±13.7 years; 52% males) of CML (89%) and MDS (11%) patients prior to (T0), 12 months after (T1), and 18 months after (T2) allogeneic HSCT. Cognitive function was examined in the domains of processing speed (Trails A; Digit Symbol Coding), attention (Digit Span), executive function (Trails B, VFT, Stroop), verbal memory (Selective Reminding Task), and motor control (Grooved Pegboard). No comparison groups were included, though impairment was noted for test scores greater than 1.4 standard deviations below normative data [65]. At T0, 81% of patients showed cognitive impairment on at least one test, with impairments primarily noted in memory (34%), motor control (32%), and executive function (16%). At T2, 36% of patients showed cognitive impairment on at least one test, and patients were significantly impaired in the domains of processing speed, motor control, and verbal memory. Younger patients, CML patients, and patients with higher baseline language performance were more likely to improve over time.

Syrjala and colleagues[86] examined a study sample (n=142; 41.5±9.3 years; 49% males) comprised of patients primarily diagnosed with CML (50%), acute leukemia (21%), and MDS (13%). Patients were assessed prior to (T0), 2.6

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months after (T1), and 12 months after (T2) allogeneic HSCT. Before study enrollment, all patients received systemic chemotherapy, with 48% receiving hydroxyurea and 12% receiving interferon, and 63% of patients received total body irradiation. Cognitive function was examined in the domains of processing speed (Digit Symbol Coding), executive function (Trails B, COWA, WCST), verbal memory (HVLT), and motor control (Grooved Pegboard). No comparison groups were included, though impairment was noted for test scores greater than 1 standard deviation below normative data. At T0, 71% of patients showed cognitive impairment, with deficits primarily noted in COWA (32%), HVLT (32%), Trails B (22%), and Digit Symbol Coding (21%). At T1, 94% of patients showed cognitive impairment, with deficits primarily noted in COWA (56%), HVLT (44%), Digit Symbol Coding (35%), and Trails B (27%). At T2, 74% of patients showed cognitive impairment, with deficits primarily noted in COWA (33%), HVLT (33%), Digit Symbol Coding (21%), and Trails B (15%). HSCT patients showed chronic impairments in COWA and HVLT performance across all study visits, and showed acute impairments at T1 in Trails B and Digit Symbol Coding performance. Patients not receiving chemotherapy or receiving hydroxyurea only were less likely to be impaired at T0. Of all patients not showing impairment at T0, 54% showed new impairment at T2.

Allogeneic/ Autologous Transplant. Harder and colleagues[87] examined a study sample (n=25; median age of 47; 64% males) comprised of patients primarily diagnosed with MM (28%) and NHL (16%). Patients were assed prior to (T0), 6 months after (T1), and 12 months after (T2) either allogeneic (76%) or

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autologous (24%) HSCT. Prior to HSCT, 40% of patients were classified as high risk disease and 80% of patients received at least one course of chemotherapy. Cognitive function was examined in the domains of processing speed (Trails A), attention (Digit Span), executive function (Stroop, Trails B, VFT), visual memory (CFT), and verbal memory (CVLT). No comparison groups were included, though impairment was noted for test scores greater than 2 standard deviation below normative data. At T0, impairments were primarily observed in the domains of processing speed, attention, and executive function. At T2, no evidence of impairment was observed, but memory performance improved relative to T0.

Meyers and colleagues[88] examined a study sample (n=61; 37.5 years; 56% males) comprised of patients primarily diagnosed with CML (43%), NHL (20%), and AML (10%). Patients were assed prior to (T0), 0.4 months after (T1), discharge (T2), and 8 months after (T3) either allogeneic (69%) or autologous (31%) HSCT. Prior to HSCT, 35% of patients received chemotherapy treatment with interferon-alpha. Cognitive function was assessed with the Dementia Rating Scale (DRS)[89], a brief cognitive screening tool developed to broadly assess cognitive functions. No comparisons groups were included, though impairment was noted for test scores greater than 2 standard deviation below normative data. Overall test performance was impaired in 20%, 13%, 23%, and 10% of patients at T0, T1, T2, and T3, respectively. DRS performance at T0 predicted changes in anxiety and depression at T2, such that higher DRS performance was associated with lower anxiety and depression at follow-up. No association was reported between cognitive function and HSCT type.

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Harder and colleagues[90] examined a study sample (n=101; 42.0±12.1 years; 61% males) comprised of patients primarily diagnosed with NHL (29%), acute leukemia (27%), chronic leukemia (17%), and MM (17%). Patients were assessed prior to (T0), 8 months after (T1), and 20 months after (T2) either allogeneic (66%) or autologous (34%) HSCT. Prior to HSCT, 98% of patients were given conditioning treatment primarily with high-dose cyclophosphamide (74%). HSCT patients were compared to a non-transplant comparison group (n=82; 39.2±13.1; 45%) comprised primarily of NHL (35%) and HD (60%) patients, most of which (90%) received chemotherapy. Cognitive function was examined in the domains of processing speed (Trails A, Digit Symbol Substitution), attention (Digit Span), executive function (VFT, Stroop, Trails B), visuospatial reconstruction (Blocks), visual memory (CFT, BVRT), and verbal memory (CVLT). Performance in both groups was compared to normative data, and scores greater than 2 standard deviations below means were noted as impaired. Prior to transplant, impaired cognitive function was observed across both groups in the domains of processing speed, visual memory, and verbal memory. Between-group differences failed to reach significance at baseline. Although no significant declines were observed across testing intervals, HSCT patients performed worse than comparison groups in the domains of processing speed, attention, and executive function.

Friedman and colleagues[91] examined a study sample (n=117; 45.4±11.9 years; 59% males) comprised of patients primarily diagnosed with NHL (30%), MM (19%), and CML (15%). Patients were assessed prior to (T0), 1.5 months

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after (T1), and 7 months after (T2) either allogeneic (49%) or autologous (51%) HSCT. Cognitive function was examined in the domains of processing speed (Trails A, Digit Symbol Substitution), attention (Digit Span), executive function (Trails B, COWA), and verbal learning (HVLT). No comparison groups were included, though test performance greater than 2 standard deviations below normative data were noted as impaired. Prior to transplant, 39% of patients showed cognitive impairment in Trails A (23%), Trails B (25%), COWA (13%), and HVLT (27%). Reliable declines in performance were found in 47% of patients at T1, and 33% of those patients showed further decline at T2. Declines in cognitive function was not predicted by transplant type, age, education, or psychosocial function.

Jacobs and colleagues[92] examined a study sample (n=388; 50.1±12.4 years; 54% males) comprised of patients primarily diagnosed with MM (63%), NHL (10%), and AML (7%). Patients were assessed prior to (T0), 6 months after (T1), and 12 months after (T2) either allogeneic (21%) or autologous (79%) HSCT. Cognitive function was examined in the domains of processing speed (Trails A, Digit Symbol Substitution), attention (CPT), executive function (Trails B; COWA; Stroop), verbal memory (CVLT), and motor control (Grooved Pegboard). No comparison groups were included, though test performance greater than 1 standard deviation below normative data were noted as impaired. Prior to transplant, 16% of patients showed global cognitive impairment, with impairments noted specifically in the domains of attention (23%), verbal memory (19%), and motor control (89%). Across cognitive domains, excluding attention,

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performance improved with time. As with other studies failing to include a comparison group, improvements in performance should not be interpreted as transplant-related improvement in cognitive function.

Autologous Transplant. Jones and colleagues[93] examined a study sample (n=53; 57.8±8.2 years; 62.3%) comprised of MM patients scheduled to undergo autologous SCT. Patients were assessed prior to (T0), 1 month after (T1), and 3 months after (T2) transplant. All patients underwent at least one induction chemotherapy cycle, and 77.1% of patients underwent at least three induction chemotherapy cycles. Most patients (86.8%) received bortezomib-based induction treatment. Cognitive function was examined in the domains of processing speed (Trails A, Digit Symbol Substitution), attention (Digit Span), executive function (Trails B, COWA), verbal memory (HVLT), and motor control (Grooved Pegboard). No comparison groups were included, though test performance greater than 2 standard deviations below normative data were noted as impaired. Prior to transplant, 47.2% of patients showed impaired cognitive function on at least one test, with impairments noted primarily in performance on Trails A (11.3%), Trails B (20.8%), COWA (20.8%), and HVLT (28.3%). At T1, 48.8% of patients showed reliable decline in cognitive performance relative to T0, with impairments noted primarily in the domains of verbal memory (29.3%) and motor control (15%). At T2, 48% of patients showed reliable decline in cognitive performance relative to T1. Of all patients showing decline at T1, 50% showed further decline at T2; of all patients not showing decline at T1, 46% showed new decline at T2. Factors that predicted declines in

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cognitive function were pre-transplant impairment, number of induction treatment cycles, education, and subjective complaints of “difficulty remembering” and “difficulty paying attention.”

Comparing Patterns of Objective and Subjective Cognitive Impairment

As noted above, there is considerable debate regarding the predictive validity of self-assessments to screen for cognitive impairment[2–6]. Similar discrepancies are present in the current literature on subjective and objective measures of cognitive function in hematological cancer patients. Evidence for chemotherapy-related cognitive impairment based on subjective measures varies based on study design. Cross-sectional studies have consistently demonstrated self-perceived cognitive impairment in post-treatment patients[39–45,53]. In contrast, longitudinal studies have consistently failed to demonstrate self-perceived cognitive impairment during[47,48] and following[46–48] treatment with respect to baseline reports. Consistent evidence for chemotherapy-related cognitive impairment has been demonstrated by studies implementing objective measures. Multiple cross-sectional studies have demonstrated cognitive impairment in post-treatment patients[40,43,52,53,66–69]. Furthermore, longitudinal studies have demonstrated cognitive impairment prior to treatment[49,70,76,78,79,85–87,91–93] and further decline in cognitive function following treatment[49,55,70,76,79,86,91,93], demonstrating direct evidence for treatment-related cognitive impairment. Some studies have failed to show treatment-related declines in cognitive function[80,87,9290]. Critically, however, these studies were constrained by lack of a

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comparison group to rule out well-documented practice effects in neurocognitive exams.

Studies directly comparing subjective and objective outcomes best demonstrate low predictive validity of self-perceived cognitive function. Of importance, these studies[40,43,53] exclusively examined lymphoma patients. Wouters and colleagues[40] demonstrated lower self-reported cognitive function in patients treated with chemotherapy. Although no significant impairment in raw objective performance was found, 16% of patients were impaired based on normative data obtained from healthy comparisons. Subjective cognitive measures were similar between impaired (16%) and unimpaired (84%) patients, failing to show a relationship between objective and subjective cognitive function. Krolak and colleagues[43] demonstrated a higher frequency of impairment on both objective and subjective cognitive measures. Although these two measures were significantly correlated, the weak correlation coefficient (r=.29) indicated subjective cognitive function accounted for only 8% of the variance in objective cognitive function. Furthermore, pain was associated with objective cognitive function whereas fatigue and anxiety were associated with subjective cognitive function, suggesting separable psychosocial factors contribute to objective and subjective function. Ahles and colleagues[53] demonstrated worse objective and subjective cognitive function in patients treated with chemotherapy compared to patients treated with local therapy. In contrast to Krolak and colleagues, correlations between objective and subjective cognitive function failed to reach significance.

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These studies demonstrate the poor predictive validity of cognitive self-assessments to screen for clinically-relevant cognitive impairment. Critically, however, these studies were cross-sectional by design, precluding the ability to evaluate the relationship between treatment-related changes in subjective and objective measures. Thus, longitudinal studies comparing objective and subjective measures are critical to evaluating whether self-assessments are sensitive to acute changes in cognitive function.

Neural Mechanisms of Cognitive Impairment

Cognitive functions studied in cancer populations emerges from dynamic patterns of neural activity in function-specific cortical regions[94,95]. Neural activity can be measured in both the spatial and temporal domain. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are two neuroimaging modalities that provide high spatial resolution measures of neural activity. MRI and PET measure brain structure and function with millimeter-level resolution, isolating putative changes to specific cortical regions. In contrast, electroencephalography (EEG) and magnetoencephalography (MEG) are two neuroimaging modalities that provide high temporal resolution measures of neural activity. EEG and MEG measure brain function with millisecond-level resolution, isolating changes in neural activity associated with specific cognitive functions. To develop more rigorous tools to evaluate cognitive function in cancer patients, chemotherapy-related changes in cognitive function must be understood through precise mechanisms affecting structural and functional changes to the brain. In the following section, studies that have utilized

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neuroimaging modalities are reviewed to place cognitive findings in biological context.

Chemotherapy-Related Changes. Two cross-sectional studies[52,96] of primarily NHL survivors have evaluated PET differences in Ctx+ patients approximately 7-months post-treatment compared to Ctx- patients. Both studies found chemotherapy-related changes in the dorsal attention network (DAN) and central executive network (CEN), a constellation of cortical regions critical to spatial attention, working memory, and executive functions[97–99]. Baudino and colleagues[52] examined patients prior to (n=18) and up to 8-months after (n=32) treatment. Neurocognitive measures of executive function (Trails B) showed greater impairment in Ctx+. PET activity was reduced in Ctx+ patients compared to HC participants; furthermore, PET activity correlated negatively with number of chemotherapy cycles and positively with time since chemotherapy, suggesting Ctx+ patients experience acute changes in brain metabolism during treatment and recovery of normal brain metabolism following treatment. Importantly, PET activity correlated with executive function, though this correlation failed to withstand correction for multiple comparisons.

D'Agata and colleagues[96] compared NHL survivors (n=14) approximately 7-months post-treatment to NHL survivors not treated with chemotherapy (n=14). Multivariate pattern classification methods revealed patterns of neural activity within DAN and CEN correctly discriminated between Ctx+ and Ctx- patients with 80% accuracy. Interestingly, average DAN activity was indistinguishable between patient groups, suggesting more information regarding chemotherapy-related

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cognitive impairment could be extracted from patterns of activity rather than overall mean activity levels. These pattern differences may be associated with well-documented age-related shifts of neural activity[100,101], in which more frontal activity may be recruited as a compensatory mechanism to overcome impairments in parietal cortex.

In one EEG study[41], NHL survivors were compared to healthy controls approximately 3-months post-chemotherapy. NHL survivors were divided into two groups based on treatment (R-CHOP, BR). Individual differences in alpha peak frequency (iAPF), a dominant neural rhythm associated with sleepiness[102,103] and cognitive function[104–106], were assessed. Higher iAPF are associated with better cognitive function, such as attention and memory[107], and are lower in traumatic brain injury patients[108]. Zimmer and colleagues[41] found no significant difference in iAPF between Ctx+ and healthy comparisons. Although BR patients trended toward lower iAPF values, suggesting greater cortical impairment compared to R-CHOP patients, NHL patients demonstrated higher iAPF values than HC, suggesting greater cortical impairment in HC. These results contradict the conclusion made by these authors, who suggested cognitive and neural function was more impaired in NHL patients, and that BR patients were more susceptible to impairment. Potential explanations for these conflicting findings include a small sample size and overall poor EEG measure of cognitive function.

Transplant-Related Changes. Three cross-sectional MRI studies[69,109,110] have examined primarily leukemia patients post-transplant to evaluate the presence of central nervous system (CNS) abnormalities. Mohrmann and

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colleagues[109] studied patients 3.6 months post-transplant. Of all patients studied, 72% showed CNS abnormalities, which were most commonly classified as cerebrovascular lesions; approximately half of all lesions developed prior to transplant. Graus and colleagues[110] studied patients 12 months post-transplant. Of all patients studied, 11% showed CNS abnormalities, which were most commonly classified as cerebral hemorrhage and metabolic encephalopathy. Patients undergoing allogeneic HSCT, when compared to patients undergoing autologous HSCT, were more likely to develop CNS abnormalities (8% vs 0.6%) and neurologic complications (13% vs 11%). Padovan and colleagues[69] studied patients 34 months post-transplant. Of all patients studied, 60% showed CNS abnormalities, which were most commonly noted in white matter tracts of frontal (76%), parietal (52%), and temporal (34%) cortices. Furthermore, 64% of patients showed neurological impairment and 37% of patients showed cognitive impairment. Importantly, medical chart reviews indicated no neurological symptoms prior to transplant, suggesting abnormalities were transplant-related. Consistent with findings from Gaus and colleagues[110], Padovan and colleagues demonstrated greater risk for allogeneic than autologous HSCT patients for CNS abnormalities (RR=3.3), neurological impairments (RR=5.0), and cognitive impairment (RR=3.3).

One longitudinal study[79] examined leukemia patients prior to (T1) and 14-months post-transplant (T2). CNS abnormalities were noted in 56% of studied patients, with 2% of patients showing new abnormalities at T2; abnormalities were most commonly noted in white matter tracts of frontal (80%), parietal (28%),

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and temporal (28%) cortex. Neurological impairments were found in 65% of patients, with 47% of patients developing new complications between T1 and T2. Transplant-related cognitive impairment was identified in 57% of patients, with verbal fluency and Stroop performance most frequently impaired. Patients receiving chemotherapy or radiation prior to transplant were at a higher risk for neurological complications.

Animal Models

Animal models provide a robust experimental design platform for investigating the neural mechanisms of chemotherapy-related cognitive impairment. Using animal models (e.g. mice, rats), investigators administer chemotherapy to systematically examine drug-induced neurotoxicity. These studies have demonstrated chemotherapy-related changes to neuronal survival and morphology[111–129], neuronal function[122,130,131], neurotransmitter function[114,130,132–141], proinflammatory cytokine levels[139–141], and cognitive function[111,114,116–118,120,142–146]. Each class of chemotherapy agents have been associated with specific patterns of neurotoxicity, which are briefly reviewed below.

Alkylating agents cause DNA damage, resulting in reduction of cell populations, particularly those that rapidly proliferate (i.e. malignant cells)[147,148]. Alkylating agents – cisplatin, cyclophosphamide, and busulfan – are commonly used to treat hematological malignancy. Impaired spatial cognition has been shown in studies of both cisplatin[111] and cyclophosphamide[114,143,144]. Cisplatin has been shown to induce morphological changes such as a reduction in

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dendritic branching[111], dendritic spine density[111,112], mitochondrial degradation[111], and neuronal apoptosis in hippocampus[112]. Cisplatin has also been associated with changes in NMDA[132,133] (N-methyl-D-aspartate) and AMPA[133] (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor expression, both of which are glutamate receptors. Cyclophosphamide has been shown to decrease neuronal growth[113,114,125], induce neuronal apoptosis[113], increase levels of neural activity in the hypothalamus[149], and reduce bone-derived neurotrophic factor (BDNF) levels[114], a nerve growth factor that promotes neuronal survival. Busulfan has been shown to induce thinning of the cerebral cortex[119], microencephalopathy[119], and inhibition of proliferation in neural progenitor cells[115].

Antimetabolites block cellular metabolic pathways, resulting in cell cycle arrest and apoptosis[150]. Antimetabolites – cladribine, hydroxyurea, methotrexate – are commonly used to treat hematological malignancy. Cladribine and methotrexate have been shown to inhibit cell proliferation[116–118,126], including microglia[126] and hippocampal cells[116–118]. Hydroxyurea and methotrexate have been shown to reduce white matter volume, including regions of the cerebellum[121] and corpus collosum[117], and increase circulating levels of proinflammatory cytokines[139,140]. Methotrexate has been associated with apoptosis of hippocampal cells[116,128], changes in synaptic plasticity-related neural activity in hippocampus[130], and impaired spatial memory[116–118,142]. Furthermore, methotrexate has been shown to induce changes in NMDA and BDNF

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expression[130], similar to what has been shown with cisplatin[132,133] and cyclophosphamide[114], respectively.

Plant alkaloids disrupt microtubule function and DNA folding, resulting in cell cycle arrest[151,152]. Plant alkaloids – vincristine, etoposide, and doxorubicin – are commonly used to treat hematological malignancy. Vincristine has been associated with reductions in axonal excitability[122] followed by axonal degeneration and demyelination[122,123], damage to hippocampal structures[120], and impairments in learning and memory[120,145,146]. Etoposide has been associated with decreased proliferation and apoptosis of neural progenitor cells[129]. Doxorubicin has been associated with reduced glutamate update in frontal cortex and dentate gyrus[135], and reduction in dopamine concentrations in frontal cortex, hippocampus, and striatum[136].

Newer classes of chemotherapy agents, including proteasome inhibitors[153] and immunomodulatory agents[154], are being developed to treat multiple myeloma. Bortezomib, a proteasome inhibitor, has been associated with peripheral neuropathy[124,131,155], affecting primarily the dorsal root ganglion[155] and sciatic nerve[124], and increasing neurophysiological activity in peripheral nerve fibers in response to innocuous spikes[131]. Furthermore, bortezomib has been associated with a decrease in plasma BDNF[134], resulting in a suppression of neuronal repair, and an increase in tumor necrosis factor-alpha (TNF-α) levels in DRG[131,141]. Thalidomide, an immunomodulatory agent, has been associated with decreases in inflammatory markers[156,157] and prevention of memory impairment[157], reduced upregulation of NMDA receptor subunits in hippocampus

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(but not prefrontal cortex) [156], decrease in dopamine metabolism and number of dopaminergic neurons[137], and decrease in serotonergic release into synaptic cleft[138].

Research Proposal

In both animals and humans, multiple studies have demonstrated detrimental effects of hematological malignancy and chemotherapy agents on neurotransmitter systems, cortical structure and function, cognition, and psychosocial status. Animal studies have demonstrated chemotherapy-related degradation in cortical structure as a result of changes in neural progenitor cell proliferation[115–118,126,129], neuronal degradation[111–114,122,123,125] and apoptosis[112,113,116,128,129], and BDNF levels critical to neuronal repair mechanisms[114,130,134]. Changes in cortical structure are preceded by changes in neurophysiological activity[122,130,131,149], which is mediated by changes in neurotransmitter metabolism and receptor expression, including glutamate[130,132,133,135], dopamine[136,137], and serotonin[138]. Changes in cortical structure and function are directly associated with impairments in spatial cognition[111,114,116–118,120,142–146].

Human studies have demonstrated chemotherapy-related degradation of cortical structures in frontal, parietal, and temporal cortex[69,79], which have primarily resulted from cerebrovascular lesions[109,110] and metabolic encephalopathy[110]. Changes in functional activity have been shown in dorsal attention and executive control cortical networks[52,96], which encompass a constellation of cortical regions that largely overlap with regions of changes.

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Numerous studies have demonstrated cognitive impairment prior to[49,70,76,78,79,85–87,91–93] and after[40,43,49,52,53,55,66–70,76,79,86,91,93] treatment, with some longitudinal studies demonstrating treatment-associated declines in cognitive function following treatment[49,55,70,76,79,86,91,93]. Impairments were noted primarily in the cognitive domains of processing speed[49,85,87,90,91,93], executive function[49,55,85–87,91–93], and memory[85,90,9249,86,91,93]. Although some studies failed to observe treatment-related changes in cognitive function[80,87,9290], these studies were also constrained by poor study design, such as a lack of comparison groups to rule out practice effects on neurocognitive exams.

Objective cognitive measures, which revealed chemotherapy-related impairments, fail to predict self-reported cognitive function[40,43,53]. In contrast, subjective cognitive impairment may be a better indication of psychosocial distress[158,159], suggesting non-overlapping mechanisms between cognitive function and awareness of cognitive function[160–162]. Indeed, quality of life studies have demonstrated chemotherapy-related changes in physical function[33,38–49], emotional function[38–41,43,44,55], cognitive function[39–45,53], and role function[33,44,46–49,60–63], including employment, social activities, and activities of daily living (e.g. driving). Importantly, overall survival was predicted by baseline cognitive function[33] and maintaining physical activity[34–37].

Currently, there exists no translational research program designed to integrate the temporal, spatial, and biological scales necessary to comprehensively study the complex system of mechanisms underlying chemotherapy-related cognitive impairment. The goal of the current dissertation

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research was to begin this program by developing an interdisciplinary translational neuroscience toolbox.

Theoretical Framework.

Identifying the biological mechanisms through which cancer pathophysiology and treatment toxicity induces cognitive impairment is critical to developing prevention and control strategies. Several reviews have attempted to develop a theoretical framework for the emergence of chemotherapy-related cognitive impairment based on animal and human breast cancer studies[163–169]. Figure 1 provides a general overview of the proposed biological mechanisms. Acknowledging limitations of chemotherapy agents crossing the blood brain barrier[163–165,167], these reviews propose peripheral activation of proinflammatory pathways circumvents the blood brain barrier by inducing neuroinflammation through microglia activation[163–168]. Subsequently, these reviews generally converge on the same inflammation-mediated mechanisms of downstream cognitive impairment: (1) structural degradation[163–165,167,168]; (2) oxidative stress on neuronal metabolism[163–165,167,168]; (3) impaired neurogenesis and neuronal repair[163,167,168]; and (4) neurotransmitter dysregulation[164–167].

The current research aimed to apply this theoretical framework of chemotherapy-related cognitive impairment to similar patterns of cognitive impairment in hematological malignancy patients. Extending this framework, the current research also aimed to identify central cognitive functions most vulnerable to the chemotherapy-induced inflammatory pathways. Impairments to

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these central cognitive functions may predict downstream impairment of additional cognitive functions.

Attention is a capacity-limited cognitive system that mediates information processing, selecting relevant information, and ignoring irrelevant information. For example, ignored information would be unavailable for memory storage. Therefore, efficient control of these attention functions would have direct consequences on downstream cognitive functions that operate only on information selected and stored online. Indeed, converging evidence in breast cancer studies support the hypothesis that chemotherapy-related cognitive impairment arises from direct insults to neural networks supporting attention[169].

Behavioral[33,49,70] and neuroimaging[52,96] studies of hematological malignancy patients collectively suggest cognitive impairment may arise from changes in the dorsal attention and executive control networks[96]. It remains unclear, however, if these brain networks are altered in pre-treatment patients because previous studies lacked prospective evaluation and non-treatment comparison groups. In contrast, chemotherapy-related cognitive impairment has been more thoroughly studied in breast cancer patients[170–176]. In neuroimaging studies of these patients, an emerging hypothesis suggests cognitive impairment may be attributable to dysfunction in the executive function network (EFN)[175,177]. EFN promotes long-range communication between frontal and parietal cortical regions[178,179], and is associated with working memory and attentional control processes[180–182]. Accumulating evidence has shown chemotherapy-related changes in: (1) cognitive measures of processing speed, attention, and working

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memory[170–173,175,176,183–185]; and (2) EFN structural morphology and functional activity[175,177,184–189]. In one study, pre-treatment breast cancer patients showed a relative decrease in functional MRI activity within superior parietal lobule (SPL) and a relative increase in functional activity in the precuneus, medial frontal gyrus (MFG), and inferior parietal lobule (IPL) during a working memory task[187]. Patients showed treatment-related reductions in SPL, MFG, precuneus, and inferior frontal gyrus (IFG) one-month and twelve-months post-treatment. Importantly, these cortical regions are associated with attentional control processes[181,190]. Thus, converging evidence between studies of breast and hematological malignancy patients suggests impairments in attentional control networks may underlie a common mechanism for chemotherapy-related cognitive impairment[73,191].

Attentional Control.

Mechanisms of attentional control modulate the processing of incoming sensory information by selecting goal-relevant information and gating goal-irrelevant information[192–195]. Selection mechanisms include shifts of spatial or feature-based attention, stimulus processing and encoding, storage in working memory, and storage in or retrieval from long-term memory. Gating mechanisms include stimulus suppression, disengaging from stimulus processing, and control over inhibitory processes. Goal-relevant information is available to the observer either externally or internally, corresponding to information in space or mind, respectively[193,194]. Furthermore, impaired attention mechanisms are associated with detrimental real-world consequences, including declines in automobile

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driving performance[196–198] and increases in crash risk[198–200]. Collectively, these cognitive mechanisms are largely responsible for controlling active mental representations, and govern the degree to which observers are engaged in their environment and goals.

Two primary cortical pathways govern attentional control mechanisms[201]. Dorsal attention network (DAN) is comprised of the intraparietal sulcus (IPS), superior parietal lobule (SPL), and frontal eye fields (FEF)[178]; these regions are retinotopically organized and coordinate the locus of spatial attention through top-down attentional control. Ventral attention network (VAN) is comprised of inferior parietal lobule (IPL), superior temporal gyrus (STG), inferior frontal gyrus (IFG), and medial frontal gyrus (MFG)[178]; these regions are involved in bottom-up stimulus processing and filtering irrelevant information. Reciprocal cortical interactions between dorsal and ventral attention networks modulate feature-selective neural activity in sensory cortex to control stimulus selection[178,179,202–205]. Populations at risk for functional impairments within attentional control networks, including older adults[101], show declines in both selection and inhibitory control mechanisms[206–210].

Attentional control functions have been associated with dopaminergic[211–214] and serotonergic[211,215–219] neurotransmitter systems. In both systems, attentional control is associated with neurotransmitter concentration[211,213,215,216], receptor function[214,217], and regulatory genes[212,218,219]. Furthermore, some studies have demonstrated a link between attentional control mechanisms and inflammatory immune responses[220–223]. For example, systemic inflammation is

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associated with impaired executive function performance[220,223], reduced visually-evoked activity in primary visual cortex[221], and dysfunctional neural activity in frontal cortex[222]. Together, these studies indicate that attentional control mechanisms are governed by cortical and systemic systems that are particularly susceptible to tumor microenvironments and chemotherapy agents, as demonstrated in previous studies of human cancer patients and animal models.

Specific Aims and Hypotheses.

In the current dissertation research, hematological malignancy patients were studied under the hypothesis that chemotherapy-related cognitive impairment are attributable to impaired attentional control processes. Due to the low temporal resolution of MRI methodologies, overlapping brain regions are commonly associated with similar tasks despite being recruited for different task-related processes and different time scales. In contrast, EEG provides a direct measure of electrophysiological neural activity with high temporal resolution, and is sensitive to the temporal evolution of attentional control processes. Furthermore, although numerous studies have demonstrated self-reported changes in quality of life and activities of daily living, there is currently no evidence-based measures for evaluating fitness to complete activities of daily living in these patients, including automobile driving and resuming/maintaining employment. This is particularly troubling, given the link between cognitive impairment and increased risk for automobile accidents[196–198,224]. According to the US Department of Transportation, approximately 86% of all workers use their primary vehicle to commute to work. Given the increased risk for hematological

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malignancy patients to experience changes in employment status,[26-28] it is critical to develop evidence-based metrics for determining if it is safe for hematological malignancy patients undergoing chemotherapy to continue driving and consequently continue working.

Hematological malignancy patients were longitudinally studied and compared to control groups during a three-month evaluation. Hematological malignancy patients were recruited from one of two targeted treatment groups: (1) patients scheduled to receive chemotherapy (Ctx+ group); and (2) patients receiving supportive care (Ctx- group). Demographically-matched healthy controls were recruited (HC group). Ctx- patients served as the chemotherapy control group, and HC participants served as the chemotherapy and cancer control group.

All participants underwent a three-month longitudinal study. Ctx+ patients completed three separate study visits: (1) any time after diagnosis but prior to receiving first treatment cycle (baseline); (2) after one treatment cycle and before the second treatment cycle (one month after baseline); (3) after three treatment cycles and before the fourth treatment cycle (three months after baseline). Ctx- and HC groups underwent three separate study visits at similar time points.

The specific aims (SA) and hypotheses (H) of this study were:

SA1. Quantify chemotherapy-related attentional control impairments in Ctx+ patients and comparison groups

H1a. Ctx+ patients will not differ from comparison groups in attentional control abilities prior to chemotherapy; following chemotherapy

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treatment, Ctx+ patients will perform worse than comparison groups without cancer or chemotherapy.

SA2. Quantify the link between chemotherapy-related attentional control impairments and electrophysiological measures of attentional control in Ctx+ patients and comparison groups

H2a. Ctx+ patients will not differ from comparison groups in EEG measures of attentional control prior to chemotherapy; following chemotherapy treatment, Ctx+ patients will differ from comparison groups without cancer or chemotherapy.

H2b. Electrophysiological measures of attentional control will be associated with behavioral measures of attentional control (as in H1b).

SA3. Quantify the effects of chemotherapy-related attentional control impairment on complex real-world behavior measured in controlled-simulations of on-road driving scenarios designed to challenge driver attentional control abilities

H3a. Ctx+ patients will not differ from comparison groups in driving performance prior to chemotherapy; following chemotherapy treatment, Ctx+ patients will perform worse than comparison groups without cancer or chemotherapy.

H3b. Simulated on-road driving performance will be associated with behavioral (as in H1a) and electrophysiological measures (as in H2a) of attentional control.

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CHAPTER 1: METHODS

Patients

Patients were recruited within UNMC Division of Hematology/Oncology from the clinics of Drs. Vijaya Bhatt, Julie Vose, Matthew Lunning, Sarah Holstein, Krishna Gundabolu, Lori Maness, Gregory Bociek, and Philip Bierman. Eligible patients were diagnosed with one of the following hematological malignancies: Myelodysplasic Syndrome (MDS), Acute Myelogenous Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Multiple Myeloma (MM), Non-Hodgkin Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), or Chronic Myelogenous Leukemia (CML).

Study Design

Patients were recruited into one of two cohorts based on their treatment plan: 1) patients scheduled to receive chemotherapy (Ctx+ group); and 2) patients receiving best support care or no treatment (Ctx- group). Additionally, we recruited a third cohort of demographically-matched healthy control (HC) participants matched to study patients on age (±5 years), years of education (±2 years), race, and gender. Ctx- cohorts served as a comparison group for the effects of chemotherapy, and HC cohorts served as a comparison group for the effects of both cancer and chemotherapy. Study cohorts completed a three-month longitudinal study comprised of three study visits. Participants in the Ctx+ group (or comparison groups) completed 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

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treatment cycles (or three-months post-baseline). Comparison subjects completed assessments at the same intervals.

Enrollment Criteria

Inclusion criteria for patients were: 1) between 19 to 80 years of age; and 2) normal or corrected-to-normal vision. Inclusion criteria for HC participants were identical in addition to being matched to patient demographics. Exclusion criteria for patients were: 1) second cancer diagnosis in addition to recent study-specific diagnosis (patients with localized skin cancer were be excluded); 2) prior radiation or chemotherapy; 3) baseline cognitive impairment (MMSE score <25); 4) patients who are critically ill or require urgent initiation of chemotherapy; and 5) patients with any other condition that may not have allowed safe participation in the study based on the clinical judgment of the treating oncologist. Exclusion criteria for HC participants included any previous cancer diagnosis in addition to all exclusion criteria for patients.

Recruitment

Patient appointments were identified in the clinic calendar. Eligibility status was confirmed with the attending oncologist or with oncology case managers. During their clinic visit, physicians or case managers informed patients of the broad study goals and procedures. Patients interested in participating were then provided verbal and written informed consent, and were scheduled for their first study visit. In some cases, due to scheduling limitations, patients were asked if they could be contacted by phone to discuss the study

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further. If interested in participating, these patients were scheduled for their first study visit, and written and verbal informed consent were provided prior to beginning study procedures. In both cases, the MMSE was administered during their first study visit to determine baseline cognitive status per exclusion criteria.

HC participants were recruited from the Mind & Brain Health Labs (MBHL) registry maintained by the Department of Neurological Sciences. The MBHL registry provides query options to search for specific demographic factors, and are comprised of individuals who have expressed interest in participating in research studies. Contacted individuals were informed of the study goals and procedures. Interested individuals were scheduled and written and verbal informed consent were provided prior to beginning their first study visit.

Study Procedures

Patients completed a 2.5-hour battery of tests designed to measure behavioral and neural mechanisms of attentional control. Broadly, this battery involved measuring scalp electroencephalography (EEG) while study participants completed computer-based cognitive tasks and driving simulation tasks. EEG measures were designed to reveal underlying neural activity evoked during cognitive and driving tasks. Clinically-validated measures were obtained for comparison, including assessments of visual function, quality of life, and neuropsychological performance.

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Quality of Life Assessment

The RAND 36-item Short Form Healthy Survey (SF-36) was developed during the Medical Outcomes Study (MOS) to measure patient assessed health-related quality of life[225–227]. SF-36 has demonstrated good validity[227] and reliability[225] in assessing physical and mental health across patient populations, including cancer survivors[228,229]. SF-36 surveys were completed to assess gold-standard measures associated with quality of life outlined below.

SF-36 is comprised of eight subscales designed to measure the following constructs[226]: (1) *Physical Functioning* – assesses degree to which physical activities are limited due to health; (2) *Role Limitations (Physical)* – assesses degree to which performance during work or other daily activities is affected by physical problems; (3) *Social Functioning* – assesses degree to which social activities are affected by physical or emotional problems; (4) *Bodily Pain* – assesses degree to which bodily pain is experienced; (5) *Mental Functioning* – assesses degree to which feelings of nervousness and depression are experienced; (6) *Role Limitations (Emotional)* – assesses degree to which performance during work or other daily activities is affected by emotional problems; (7) *Fatigue* – assesses degree to which patient feels full of energy or is fatigued; (8) *General Health* – assesses perception of general health.

SF-36 construct validity has demonstrated ability to discriminate physical and mental health problems in patients with medical and psychiatric diseases, respectively[227]. Each construct was assessed on its ability to discriminate disease *severity* (low/high) for medical and psychiatric diagnoses, and

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incremental disease burden for either medical (high medical severity plus psychiatric diagnosis) or psychiatric (high psychiatric severity plus medical diagnosis) diagnoses. Physical Functioning construct demonstrated high validity for medical severity and incremental (1.0). Role Limitations (Physical) construct demonstrated high validity for medical severity (.71) and medical incremental (.56). Social Functioning demonstrated strong validity for psychiatric disorder (.54), and moderate validity for medical severity (.35), psychiatric severity (.32), and psychiatric incremental (.34). Bodily Pain demonstrated moderate validity for medical severity (.27) and psychiatric incremental (.34). Mental Health demonstrated strong validity for psychiatric severity and incremental (1.0). Role Limitations (Emotional) demonstrated strong validity for psychiatric disorders (.54), and moderate validity for psychiatric severity (.43) and psychiatric incremental (.34). Vitality demonstrated strong validity for medical severity (.67), and moderate validity for psychiatric severity (.31) and psychiatric incremental (.22). General Health demonstrated strong validity for medical severity (.99) and medical incremental (.68), and moderate validity for psychiatric incremental (.26).

Neuropsychological Assessment

Four assessments were selected to measure processing speed, attention, working memory, and executive control. The following measures were selected because they are gold-standard neuropsychological tests that have been used extensively to assess cognitive function patients diagnosed with neurological diseases.

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Trail Making Test. Trail Making Test (TMT)[230–233] involves drawing lines between 25-items randomly distributed on a page, where each consecutively drawn line connects two items in ascending order. TMT is comprised of two testing formats: (1) Trails A assesses processing and motor speed; and (2) Trails B assesses executive control in addition to abilities assessed in Trails A. During Trails A, test items are numbers ranging from 1 to 25, and participants complete the task by drawing a line between items in ascending number order (e.g. 1-2, 2-3, 3-4, etc.). During Trails B, test items are numbers (ranging from 1 to 13) and letters (ranging from A to L), and participants completed the task by drawing a line between numbers and letters in alternating ascending order (e.g. 1-A-2-B-3-D). Participants were instructed to complete the test as quickly as possible without lifting their pencil from the paper. If line segments were completed out of order, participants were corrected and an error was noted for each incorrect segment. Primary outcome measures for Trails A and Trails B were completion time and errors made.

TMT was designed to measure attention, processing speed, and mental flexibility. Reliability estimates for Trails performance are moderate (>.4) [234–236]. Similar performances in Trails A and Trails B suggest overlapping mechanisms are recruited across subtests[237–239]. Trails performance is correlated with performance in other measures of processing speed[239,240], visuo-motor scanning[241], and executive control[242,243]. Neural correlates of Trails performance have been demonstrated in frontal cortex[244,245], specifically the dorsolateral prefrontal cortex[246].

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Golden Stroop Test. Stroop test[247,248] involves rapidly verbalizing a list of color names within a 45-second time limit. Color names were limited to blue, red, and green. Stroop is comprised of three testing formats: (1) Stroop-W assesses word processing speed; (2) Stroop-C assesses color processing speed; and (3) Stroop-CW assesses executive control. During Stroop-W, the color name list was provided as typed words (i.e. RED, BLUE, GREEN) printed in black ink, and participants were asked to read the words as quickly as possible. During Stroop-C, the color name list was comprised of typed XXXX's printed in colored ink, and participants were asked to name the ink color as quickly as possible. During Stroop-CW, the color name list was comprised of typed words in colored ink, and participants were asked to name the ink color – not read the word – as quickly as possible; words and ink color never matched for any given test item. If participants provided the wrong color name, no feedback was provided and the item was marked as incorrect. Primary outcome measures for Stroop were number completed and errors made.

Stroop was designed to measure cognitive control over maintaining task goals and suppressing habitual responses. Reliability estimates for Stroop performance are high (>.7)[249], and within-test validity is moderate[250]. Stroop performance is correlated with performance in other measures of processing speed[251–253], working memory[251,254], and fluid intelligence[255]. Neural correlates of Stroop performance have been demonstrated in frontal cortex[256,257], specifically prefrontal cortex[258], lateral prefrontal cortex[259–261], and anterior cingulate cortex[259–261].

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Paced Auditory Serial Addition Task. Paced Auditory Serial Addition Task (PASAT)[262,263] involves systematically adding together a sequence of 37 numbers listed in a recording at a presentation rate of one number every 2.4 seconds. PASAT measures processing speed and working memory. Participants were instructed to add the numbers in pairs, such that each number should be added to the number presented just before it. For example, the answer to the number sequence 5-7-2-9-6 would be 12-9-11-15 (i.e. 5+7, 7+2, 2+9, 9+6). If participants missed the addition of a given number pair, they were instructed to continue adding once they heard the next two numbers. If participants incorrectly added a given number pair, no feedback was provided and the item was marked as attempted but incorrect. Primary outcome measures for PASAT were number attempted, number correct, and number incorrect or missed.

PASAT was designed to measure working memory, divided attention, and information processing speed. Reliability estimates for PASAT performance are high (>.73) [264,265], and within-test validity is high (>.86) [266]. PASAT performance is correlated with performance in other measures of information processing[267,268], attention[251,267,269], sustained attention[270], divided attention[271,272], and working memory[267,268]. Neural correlates of PASAT performance have been demonstrated in frontal and parietal cortical regions critical to attention and working memory performance[273].

Useful Field of View. Useful Field of View (UFOV)[274] is a computer-based task that involves rapidly processing information briefly presented within a stimulus display and reporting what was processed in a subsequent test display.

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UFOV is comprised of three testing formats, each named after the cognitive function assessed: (1) Processing Speed; (2) Divided Attention; and (3) Selective Attention. During the Processing Speed task, a single object was presented within a central white box during the stimulus display, and participants were instructed to indicate whether the central object was a car or truck during the test display. During the Divided Attention task, stimulus displays were identical to the Processing Speed stimulus displays with the addition of a single object presented in the periphery; the peripheral object was presented in one of 8 locations uniformly spaced around an imaginary circle. In the test display, participants were instructed to indicate both whether the central object was a car or truck and where the object was presented in the periphery. During the Selective Attention task, stimulus displays were identical to the Divided Attention stimulus displays with the addition of multiple triangle objects designed; test displays were identical to the Divided Attention test displays. Task performance was measured by systematically changing stimulus display duration based on response accuracy; if responses were correct (or incorrect), the subsequent stimulus display was presented for a shorter (or longer) duration. Task administration ended when responses were correct 75% of the time, resulting in a stimulus detection threshold quantified as stimulus display duration. Primary outcome measures for UFOV were stimulus detection thresholds for each task.

UFOV was designed to measure visual function impairments. Reliability estimates for UFOV performance are high (>.7) [275], and is sensitive to visual field defects[224,276] and driving performance[277,278]. UFOV performance is correlated

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with performance in other measures of processing speed[279–281], attentional control[281,282], attentional disengagement[283], and executive function[284].

Computer-Based Cognitive Tasks

Two computer-based cognitive tasks were selected to measure attentional control function. *Capture tasks*[285–289] measure processes related to inhibitory control and disengagement speed; response time is the primary outcome measure. This task manipulates multiple stimulus conditions to: 1) examine the degree of inhibitory control required to ignore distracting information and 2) resolve the speed at which attention can disengage from distracting information. *Filtering tasks*[210,290] measure processes related to inhibitory control and storage capacity; response accuracy is the primary outcome measure for this task. This task manipulates multiple stimulus conditions to examine: 1) how much information can be stored in mind and 2) the degree of inhibitory control required to ignore distracting information.

During each task, participants were seated at an eye-to-screen distance of 58cm from the stimulus presentation display. Stimulus displays were created in MATLAB using the Psychophysics Toolbox. Stimulus dimensions are given in degrees of visual angle (°) and stimulus colors are given in RGB values.

Capture Task and Procedures.

Figure 2A provides an overview of the Capture Task. Each display contained four placeholders (1.7°x1.7°; 0.1° line thickness) subtending 3.6° from a black [0,0,0] central fixation dot (diameter=.4°), and were rendered against a gray [128,128,128] background. Placeholders were fixed at uniformly separated

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locations centered in each quadrant. In task-irrelevant cue displays, a set of four dots (diameter=.2°) were presented at fixed locations around each placeholder, each subtending 1.0° center-to-corner for each placeholder. In search displays, four Landolt squares (1.0°x1.0°), each with 0.15° line thickness and 0.6° gap size, were centered in each placeholder. For each search display, Landolt square color (red [256,0,0], green [0,256,0], blue [0,0,256], yellow [256,256,0]), orientation (0°, 90°, 180°, 270°), and placeholder assignment were randomly sampled without replacement.

Task procedures for a given trial are depicted in Figure 2A. Prior to beginning the experiment, participants were assigned a target color (e.g. red). Each trial started with a blank placeholder display for a variable inter-trial interval (ITI). ITI values were randomly sampled from a uniform distribution ranging from 750-milliseconds to 1500-milliseconds in increments of 50-milliseconds. Next, the task-irrelevant cue display was presented for 50-milliseconds. For a given trial, one of three possible cue conditions were rendered: (1) Neutral (50% of trials): all placeholder dots were rendered in black; (2) Singleton (25% of trials): one set of placeholder dots were rendered in a non-target color (e.g. green, blue, yellow); (3) Contingent (25% of trials): one set of placeholder dots were rendered in the target color (e.g. red). Cue and search displays were separated by a blank inter-stimulus interval (ISI) display for a randomly sampled duration of 50, 150, 250, or 350-milliseconds. Following the blank ISI display, the search display was presented until participants responded

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with a button press. Participants pressed either the up, down, left, or right array keys when the target orientation was 0°, 180°, 270°, or 90°, respectively.

Participants completed a total of 256 trials. The following conditions were counterbalanced across trials: cue condition, cue location, ISI duration, target location, and target orientation. Experimenters instructed participants to maintain fixation and refrain from initiating blinks or eye movements to the best of their abilities (see EEG procedures below). Experimenters instructed participants to respond as quickly and accurately as possible.

Response time (RT) was the primary behavioral outcome measure. For each trial, RT was measured as the temporal delay between the onset of task-irrelevant stimulus display and button press. Aggregate RT distributions were inspected individually for each participant. Incorrect trials and trials containing RT values more than 3 standard deviations greater than the mean of aggregate RT distributions were removed from further analysis[1]. Remaining RT values were then binned and averaged for each cue condition. Response time costs (d') were estimated between cue conditions to determine how cue identity affected performance. For any two conditions, response time cost was estimated as: $RT_{cost} = [(X_{(1)} - X_{(2)})/\sigma_{(12)}^2]$, where $X_{(1)}$ is average RT for condition 1, $X_{(2)}$ is average RT for condition 2, and $\sigma_{(12)}^2$ is standard deviation of RT values across conditions 1 and 2. Three RT cost comparisons were computed: (1) singleton to

[1] Of all RT values collected, only 0.88% were more than 3 standard deviations outside the mean of aggregate RT distributions. Thus, less than 1% of RT data were lost during outlier removal procedures.

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neutral (*singleton d'*); (2) contingent to neutral (*contingent d'*); and (3) contingent to singleton (*contingent-singleton d'*).

Filter Task and Procedures.

Figure 2B provides an overview of the Filter Task. Each stimulus display contained a central black fixation dot (diameter=.4°) presented against a gray [128, 128, 128] background. Cue displays contained a black arrow (1.1°x3.3°) that was oriented towards the left or right side of fixation. Memory displays contained rectangular stimuli (0.6°x1.7°) that varied in number and color. Target items were red [256,0,0], and distractor items, when present, were blue [0,0,256] or green [0,256,0]. Target number (1 item, 3 items) and distractor number (0 items, 2 items) were counterbalanced, producing the following four stimulus conditions: (1) Load-1: one red target item and no distractor items; (2) Load-3: three red target items and no distractor items; (3) Filter-1: one red target item and two distractor items; and (4) Filter-3: three red target items and two distractor items. Two sets of task stimuli were presented, where one set was presented to the left of fixation and one set was presented to the right of fixation. Stimulus locations were constrained to areas outside of a central region (13.1°x8.2°) and within a peripheral region (13.1°x16.3°) centered over fixation, and center-to-center distances between each stimulus were greater than 2.4°. Each set of stimulus orientations were randomly oriented at 0°, 45°, 90°, or 135°, with the constraint that no two target items were the same orientation and no more than two total items were the same orientation. For test displays, a single red test stimulus was presented in a randomly sampled target location. Test stimulus

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orientations were either the same or different with respect to the orientation of the probed target item presented in the same location during memory displays.

Participants were instructed to remember the orientation of each red target item presented within the cued side of fixation. Task procedures for a given trial are depicted in

Figure 2B. Each trial started with a blank display for a variable ITI that was randomly sampled from a uniform distribution ranging from 750-milliseconds to 1500-milliseconds in increments of 50-milliseconds. Next, a cue display was presented for 200 milliseconds to indicate which set of target items would be tested. For trials in which the cue was oriented to the left (or right) side of fixation, participants were instructed to remember the left (or right) target items. Next, a blank display was presented for variable ISI that was randomly sampled from a uniform distribution ranging from 300 to 600 milliseconds in increments of 100 milliseconds. Blank ISI displays were followed by a 200-millisecond memory display. Following a 900-millisecond blank display, a test display was presented until a response was made. Participants responded by pressing the “z” or “/” key when test and probed stimulus orientations were different or the same, respectively.

Participants completed a total of 256 trials. The following conditions were counterbalanced across trials: cue orientation, target number, distractor number, and test stimulus orientation. Experimenters instructed participants to maintain fixation and refrain from initiating blinks or eye movements to the best of their

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abilities (see EEG procedures below). Experimenters instructed participants to respond as accurately as possible.

Response accuracy was the primary behavioral outcome measure. For each trial, correct and incorrect responses were coded as a 1 and 0, respectively. Trial accuracy values were then binned and averaged for each condition. Load-dependent and filter-related changes in response accuracy were estimated by subtracting accuracy in the Load-1 condition from accuracy in the Load-3 and Filter-1 conditions, respectively. Thus, load-dependent changes reflect reductions in response accuracy associated with storing additional *relevant* items, and filter-related changes reflect reductions in response accuracy associated with storing additional *irrelevant* items.

Driving Simulation

Driving Simulator. SENSEI (Simulator for Ergonomics, Neuroscience, Safety Engineering and Innovation; Figure 3A), a DriveSafety (Salt Lake City, UT) RS-600 Research Simulator, is a fully integrated, high performance, high fidelity driving simulation system with an authentic automotive cab designed for use in ground vehicle design and driving safety research applications. Coupled with HyperDrive advanced scene and scenario authoring tools, the SENSEI simulation system provides an ideal environment to create purpose-built driving scenarios for a wide range of research studies. The RS-600 provides an out-the-window display environment of 290 degrees with 7 Ultra-HD (3840x2160 each) curved LED displays, a full-size automobile cab including windshield, front and rear seating compartments, center console, dash and instrumentation, automatic

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transmission gear select, two side and one center rear view LCD mirrors. The car cab is based on a 2004 Ford Focus. This system provides a flexible and advanced data collection capability for recording vehicle and driver performance measures.

In addition to measuring general driving performance, participants completed two tasks designed to recruit distinct attention abilities. *Car following tasks*[291,292] involve maintaining a constant distance relative to a lead vehicle while avoiding lead vehicle incursion; this task requires rapidly processing information in the environment, suppressing irrelevant information such as pedestrians and other vehicles, and enhance relevant information presented by the lead vehicle such as braking or accelerating. *Visual search task*[293–297] involves rapidly shifting attention within a visual display to find a target item; this task requires rapidly processing information, deploying attention between objects, suppressing irrelevant information, and enhancing target information within visual displays.

Visual Search Task and Procedures. Visual search task required drivers to respond with the identity of a red target Landolt square stimulus presented among black distractor Landolt square stimuli. Stimulus configurations are depicted in Figure 3B. Eight square placeholders (diameter=2.0° visual angle) were rendered in white and presented around an imaginary concentric circle (radius=7.3°) centered over a .8° white fixation dot. Each placeholder location was separated by 22.5°, starting at 22.5° and ending at 337.5°. Landolt square stimuli (diameter=1.7°) were rendered with line thickness of .2° and a .6° gap centered on one side. Each stimulus display was comprised of 7 black distractor

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Landolt squares and 1 red target Landolt square. Distractor squares were rendered in black with the gap on any one side of a given square, and target squares were rendered in red with the gap on either the left or right side of the square.

Each trial started with the presentation of the square placeholders to cue trial initiation. Following a 50-millisecond cueing period, the stimulus display was presented until a response was made. Drivers were instructed to indicate whether the gap was on the left or right side of the target square by pressing the left or right steering wheel button, respectively. Following each response, placeholder and stimulus displays were removed for an inter-stimulus interval (ISI) period randomly sampled with replacement from values ranging between 1 and 3 seconds in increments of 1/60th of a second. Target position and target direction were counterbalanced across a total of 48 trials.

Drivers completed visual search task under two conditions: stationary (low load) and driving (high load). In the stationary condition, visual search displays were presented against a black background and central fixation was visible; in the driving condition, visual search displays were presented against the naturalistic background (Figure 3B) while drivers traveled along a straight rural road.

Car Following Task and Procedures. Car following task required drivers to maintain a two-car length distance (18 meters) behind a lead vehicle (LV) for 360 seconds[291]. LV velocity fluctuated pseudo-randomly across time based on the value of a complex signal at time *t*. Complex signals were created by estimating

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the weighted linear sum of three randomly sampled sinusoids with a baseline of 88.5 km/h (55 mph). Each sinusoid had an oscillatory frequency of .033, .083, and .117 Hz and an amplitude of 9.770, 3.888, and 2.779 km/h, respectively. For each driver, phase values for the second and third sinusoid were randomly sampled from a uniform distribution ranging from 0 to 2π radians in increments of $\pi/180$ radians; phase values for the first sinusoid were constrained such that the value of the complex signal at time t=0 would be equal to baseline (88.5 km/h).

The car following task was interleaved within a pre- and post-task baseline drive for 500 meters at a constant speed of 24.6 m/s. The sequence of events leading up to the pre-task baseline drive were as follows. First, drivers were instructed to follow the LV at a two-car length distance. Next, the LV was triggered to begin modulating its speed, depending on the driver's following distance. If driver distance was greater than 18 meters, LV velocity decreased and the driver was instructed to follow at a closer distance. If driver distance was less than 18 meters, LV velocity increased and the driver was encouraged to maintain that distance. When LV velocity reached 24.6 m/s, the pre-task baseline drive began.

Driving Scenario. Drivers were seated approximately 2.74 meters from the central simulator display. Simulator adaptation was implemented first to prevent simulator adaptation syndrome; simulator adaptation involved driving through a suburban roadway (1.95 kilometers; 40.2 km/h speed limit) and stopping at a total of four 4-way intersections. Next, three task segments within the driving scenario were completed in the following sequence: (1) the visual search task

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was completed during the initial segment of a rural highway with an 88.5 km/h speed limit; (2) a baseline driving segment was completed on the same rural highway following visual search task completion; (3) the LV pulled out in front of the driver's right side of the road; (4) the car following task was completed; (5) the LV came to a complete stop, ending the driving scenario. Driving simulation took approximately 20 minutes to complete.

EEG Acquisition and Analysis

EEG was recorded during cognitive tasks and driving simulation tu study neural mechanisms of attention on a millisecond timescale. Three electrophysiological components were selected to isolate distinct neural mechanisms of attention. *N2pc* components[298–300] measure neural activity associated with spatial shifts of attention; this component was used to track whether attention resources are deployed during task-irrelevant cues during the Capture Task. CDA components[210,290,301] measure neural activity related to distractor suppression and online storage; this component was used to track online storage load and efficiency of filtering irrelevant items during the Filter Task. Eye fixation-related potential (EFRP) components[302–304] measure information processing capacity during naturalistic eye movements; this component was used to track information processing capacity during driving simulation.

EEG was recorded using a NeuroScan NuAmps (Compumedics) digital amplifier and silver-chloride electrodes distributed in a fitted elastic cap according to the International 10-20 System. EEG was measured from 8 scalp locations (O1, O2, PO1, PO2, P3, P4, P7, P8) with a ground reference electrode at the AFz site. Electrooculography (EOG) was recorded using a bipolar montage. Horizontal EOG (HEOG) was recorded from electrodes placed 1cm outside the

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lateral canthus of each eye to measure eye movements; vertical EOG (VEOG) was recorded from electrodes placed above and below the left eye to measure blinks. Impedances of all electrodes were maintained below 10 kΩ. EEG signals were digitized at a sampling rate of 1000 Hz and re-referenced offline to mathematically averaged left and right mastoids (A1-A2). Stimulus event triggers were sent to the EEG amplifier from the parallel port of a dedicated stimulus presentation computer. Continuous EEG measurements were recorded and monitored on a dedicated acquisition laptop. Timing delays between stimulus presentation and event triggers were measured using an analog photometer and corrected during analysis.

EEG recordings were analyzed using EEGLab[305] and ERPLab[306] MATLAB toolboxes. EEG recordings were high (.01 Hz)- and low (30 Hz)-pass filtered using a 2nd order Butterworth filter. Artifact detection routines marked continuous EEG segments contaminated by blinks or eye movements in VEOG or HEOG recordings, respectively. Blinks were detected when peak-to-peak amplitude exceeded 100 μV within a 200-millisecond sliding window and 50-millisecond step size. Eye movements were detected when the absolute difference between averaged HEOG activity exceeded 100 μV within a 400-millisecond sliding window with 10-millisecond step size. EEG segments containing artifacts were removed from further analysis.

Event-Related Potentials. For EEG data collected during Capture and Filter Tasks, ERP epochs were extracted after the presentation of each stimulus display with a pre-stimulus baseline period of 200 milliseconds. Contralateral (or

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ipsilateral) waveforms were created by averaging ERP epochs from right electrodes (e.g. O2, PO2, P4, P8) when the stimulus cue was presented in the left (or right) visual hemifield, and from left electrodes (e.g. O1, PO1, P3, P7) when the stimulus cue was presented in the right (or left) visual hemifield. Difference waveforms were created for each electrode pair (O1/O2, PO1/PO2, P3/P4, P7/P8) by subtracting ipsilateral waveforms from contralateral waveforms. Difference waveforms were visually inspected across all electrodes pairs.

For the capture task, ERP waveforms were measured in PO1/PO2 and O1/O2 electrode pairs and inspected 0-400 milliseconds after cue display onset. N2pc amplitudes, which are sensitive to spatial shifts of attention towards the task-irrelevant cue, were measured by averaging ERP activity from 230 to 280 milliseconds following cue onset. For the filter task, ERP waveforms were measured in PO1/PO2 and P3/P4 electrode pairs and inspected 0-1100 milliseconds after memory display onset. CDA amplitudes, which are sensitive to changes in online working memory storage load, were measured by averaging ERP activity from 400 to 1000 milliseconds following memory display onset.

Eye Fixation-Related Potentials. To study neural correlates of information processing during naturalistic eye movements, eye fixation-related potentials (EFRP) were measured during driving simulation with unconstrained eye movements. EFRP waveforms were measured from EEG recordings during baseline driving using the following methods.

EEG recordings were then extracted 3- to 240-seconds after the driving visual search task (Task 2) was completed. HEOG recordings were used to

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measure eye movements. Saccade offset events were created for timepoints meeting all of the following criteria: (1) for 30 milliseconds of HEOG activity preceding time *t*: R^2 and β parameter of best fitted regression line were greater than .9 and 2.0 uV/ms, respectively; (2) for 150 milliseconds of HEOG activity after time *t*: root mean squared (RMS) of residuals and β parameter of best fitted regression line were less than 20 and 2.0 uV/ms, respectively; (3) difference between β parameters for both regression lines were greater than 2.0 uV/ms.

EFRP epochs were extracted 0 to 400 milliseconds after each saccade offset event with a 100-millisecond baseline period. Saccade amplitude was estimated as the absolute difference between HEOG activity observed -150 to -100 milliseconds prior to and 0 to 50 milliseconds following saccade offset events [302]. Individual waveforms were analyzed only for epochs with saccade amplitudes within the range of 100-400 μV [302] and EEG peak-to-peak amplitudes less than 160 μV. P1 amplitudes were measured from O1 and O2 electrodes by averaging EFRP activity $\pm$50 milliseconds relative to peak amplitude observed 80-120 millisecond after saccade offset.

Data Analysis

Categorical data were descriptively summarized using frequency and percentage tables, and numeric data were descriptively summarized using means and standard deviations. Univariate graphs were created for predictor and response variables to investigate distributional properties. Between-group differences in group demographic characteristics were assessed using chi-squared tests for categorical variables (e.g. gender) and independent-samples t-

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tests for numeric variables (e.g. age). Between-group differences and within-group changes in repeated measures were assessed using generalized linear mixed models. Models were constructed to account for effects of age and education. Repeated measures were modeled using a compound symmetry covariance structure. Kenward-Roger degrees of freedom corrections were used to account for missing data[307]. 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.

Statistical analyses were performed with SAS Studio 3.6 (SAS Institute Inc.). Chi-squared tests were performed using PROC FREQ, and t-tests were performed using PROC TTEST. Generalized linear mixed models were performed using PROC MIXED, and the PDIFF command was implemented to evaluate post-hoc comparisons.

For the purposes of this dissertation, given its sample size, results were interpreted with a $p<.20$ significance level. This threshold was chosen to identify outcome measures to be included in future large-scale confirmatory studies.

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CHAPTER 2: STUDY SAMPLE

Sample Characteristics

45 participants (15 per group) were enrolled into the study between November 8, 2016 and September 27, 2017. The complete study sample was comprised of participants that were 60.8±14.5 years of age (22-80 years), 47% male, 98% Caucasian, 86% right-handed, 64% married, and had 13.9±1.5 years of education. Summary statistics for demographic measures are presented for each group in

Table 1. Omnibus between-group analyses did not show evidence of an effect for demographic measures of 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, and marital status ($\chi^2_{(2)}$=1.33, p=.51). These results indicate that groups were well balanced across demographic dimensions.

MMSE was used to assess evidence for baseline cognitive impairment. MMSE performance across groups was 29.2±1.3. Between-group differences in MMSE performance did not show an effect ($F_{(2,40)}$=0.46, p=.64). In addition, 32% of participants self-reported normal visual function, and self-reported visual function did not show evidence of group effects ($\chi^2_{(2)}$=0.44, p=.81).

Across cancer groups (Ctx+, Ctx-), patients were diagnosed with NHL (n=16; Ctx+=10, Ctx-=6), MDS (n=7; Ctx+=1, Ctx-=6), AML (n=3; Ctx+=3), ALL (n=1; Ctx+=1), CLL (Ctx-=2), and MM (n=1; Ctx-=1). Ctx+ patients received R-CHOP (n=5), Decitabine (n=3), CHOP, BR (bendamustine rituximab), EPOCH-R

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(etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine).

Study participants were prescribed an average of 3 medications, and polypharmacy (≥4 medications) was noted in 47% of Ctx+ patients, 47% of Ctx- patients, and 40% of HC participants. Medications were further evaluated to determine the frequency at which study participants were prescribed medications known to alter brain and cognitive function (e.g. anti-convulsants, opioids, corticosteroids, neurotransmitter antagonists, sedatives). Approximately 47% of patients in both Ctx+ and Ctx- groups were taking at least one of these medications, compared to only 20% of HC participants; and approximately 27% of Ctx+ patients, 20% Ctx- paients, and 7% of HC participants were taking at least two of these medications.

Of 7 patients within the Ctx+ group: 3 patients were taking corticosteroids only; remaining patients were taking combinations of: (1) sedative and anti-convulsant; (2) corticosteroid and sedative; (3) anti-convulsant, corticosteroid, and opioid; (4) opioid, corticosteroid, and sedative. Of 7 patients within the Ctx- group: 4 patients were individually prescribed an anti-convulsant, opioid, corticosteroid, or sedative; 1 patient was taking an opioid and neurotransmitter agonist; 2 patients were taking a combination of an anti-convulsant, corticosteroid, and sedative with either an opioid or neurotransmitter agonist. Of 3 participants within the HC group: 2 participants were individually prescribed an anti-convulsant or neurotransmitter agonist; 1 participant was taking an opioid, neurotransmitter agonist, and sedative.

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Study Completion

30 (67%) study participants completed all study visits. Of the 15 participants that withdrew from the study, 7 were Ctx+ patients (47% drop rate), 5 were Ctx- patients (33% drop rate), and 3 were HCs (20% drop rate). No significant difference in drop rate was observed between groups ($\chi^2_{(2)}$=2.45, p=.29). Of the 7 dropped Ctx+ patients, 1 was an ALL patient (100% of ALL sample), 3 were AML patients (100% of AML sample), and 3 were NHL patients (30% of NHL sample). Of the 5 Ctx- patients that withdrew, 1 was a CLL patient (50% of CLL sample), 3 were MDS patients (50% of MDS sample), and 1 was an NHL patient (17% of NHL sample). Reasons for study withdraw 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).

Visit 1 completion included 14 Ctx+ patients, 14 Ctx- patients, and 15 HCs (96% completion rate); 1 Ctx+ and 1 Ctx- patient withdrew due to time constraints. Visit 2 completion included 9 Ctx+ patients, 11 Ctx- patients, and 13 HCs (73% completion rate); 4 Ctx+ patients withdrew (treatment elsewhere=1, time constraints=1, stroke=1, travel constraints=1) and 1 Ctx+ patient missed visit 2 due to illness, 3 Ctx- patients withdrew (stroke=1, stopped responding=1, time constraints=1), and 2 HCs withdrew (stopped responding=1, time constraints=1). Visit 3 completion included 8 Ctx+ patients, 10 Ctx- patients, and 12 HCs (67% completion rate); 2 Ctx+ patients withdrew (hospice=1, pain=1), 1 Ctx- withdrew (started chemotherapy), and 1 HC withdrew (travel constrains).

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Patients who withdrew from the study were less educated (13.4±1.2) than patients who completed the study (14.1±1.6) ($F_{(1,41)}$=1.99, p=.17). Patients who either completed or withdrew from the study did not differ with respect to age ($F_{(1,43)}$=1.55, p=.22), gender ($\chi^2_{(1)}$=0.40, p=.53), marital status ($\chi^2_{(1)}$=0.19, p=.66), or MMSE score ($F_{(1,41)}$=.33, p=.57).

Organization of Results Chapters

Unforeseen challenges were presented by patients and study methods during data collection, particularly for driving simulation measures. Across study visits, patients enrolled in the study were unable to complete driving simulation due to simulator adaptation syndrome (11%), inpatients unable to travel to lab (6%), time constraints during study visit (23%), technical difficulties (4%), and lack of driving experience (3%). Due to the volume of missing data, driving simulator measures were analyzed as a cross-sectional sample averaged across visits with valid data.

Results chapters were segregated into one chapter comprised of repeated measurements collected from cognitive (Specific Aim 1) and electrophysiology (Specific Aim 2) methods, and one chapter comprised of cross-sectional measurements collected from driving simulation methods (Specific Aim 3).

Protocol Assessment

Upon completing the study, patients were asked for any feedback. In general, patients provided positive feedback. The most common complaints were difficulty of PASAT and filter task, nausea during driving simulation, and traveling

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demands to and from the study site. 89% of patients agreed to enroll in a research registry to continue aiding research efforts in the future.

Data loss was a primary issue of concern for this study. Reasons for data loss were related to unreturned questionnaires, time constraints during visits, task difficulty, mobility constraints, technical difficulties, and EEG cap availability. In future studies, measures should be taken to reduce data loss. Questionnaires should be completed by study participants during their study visit, which should minimize data loss for questionnaires. To minimize data loss due to time constraints, study participants should be given the option to divide their study visits across multiple sessions. PASAT and Filter tasks were the most difficult task for patients to complete, though data loss was minimal; future studies should evaluate continued difficulty in these tasks to determine whether removal or modification is necessary. Technical difficulties were likely due to this being a pilot study that required troubleshooting new tools and methods; technical issues should continue to be monitored.

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CHAPTER 3: NEUROCOGNITIVE RESULTS

Baseline Assessment

Quality of Life

Eight outcome measures were obtained from the SF-36 survey: 1) *General Health* – perception of general health; 2) *Physical Function* – how physical activities are limited due to health; 3) *Emotional Function* – how feelings of nervousness and depression are experienced; 4) *Social Function* – how social activities are affected by physical or emotional problems; 5) *Role Function – Physical* – how performance during work or other daily activities is affected by physical problems; 6) *Role Function – Emotional* – how performance during work or other daily activities is affected by emotional problems; 7) *Fatigue* – how much patient feels full of energy or are fatigued; 8) *Pain* – how much bodily pain is experienced. Descriptive summaries of quality of life outcome measures are presented in

Table 2.

Of the 43 participants (Ctx+=14, Ctx-=14, HC=15) who completed baseline assessment, 9 failed to return quality of life assessments (Ctx+=4, Ctx-=4, HC=1). Impaired General Health was reported in 20% of Ctx+ patients, 50% of Ctx- patients, and 0% of HC participants ($\chi^2_{(2)}$=10.7, p=.005). Impaired Physical Function was reported in 70% of Ctx+ patients, 30% of Ctx- patients, and 14.2% of HC participants ($\chi^2_{(2)}$=8.23, p=.016). Impaired Emotional Function was reported in 30% of Ctx+ patients, 10% of Ctx- patients, and 0% of HC participants ($\chi^2_{(2)}$=5.91, p=.052). Impaired Social Function was reported in 40%

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of Ctx+ patients, 40% of Ctx- patients, and 14.2% of HC participants ($\chi^2_{(2)}$=2.79, p=.25). Impaired Role Function - Physical was reported by 40% of Ctx+ patients, 10% of Ctx- patients, and 7.1% of HC participants ($\chi^2_{(2)}$=4.52, p=.10). Impaired Role Function - Emotional was reported by 40% of Ctx+ patients, 20% of Ctx- patients, and 0% of HC participants ($\chi^2_{(2)}$=8.22, p=.016). Pain symptoms were reported by 50% of Ctx+ patients, 40% of Ctx- patients, and 14.3% of HC participants ($\chi^2_{(2)}$=4.0, p=.14).

Significant effects of group were found for General Health ($F_{(2,29)}$=3.4, p=.047), Physical Function ($F_{(2,29)}$=4.60, p=.018), Emotional Function ($F_{(2,29)}$=4.43, p=.021), Role Function - Emotional ($F_{(2,29)}$=4.16, p=.026), Pain ($F_{(2,29)}$=3.18, p=.057), and Role Function – Physical ($F_{(2,29)}$=1.91, p=.17). Post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups on Physical Function (-35.0±17.2; t_{29}=-2.04, p=.051), Emotional Function (-13.0±9.0; t_{29}=-1.45, p=.16), Role Function - Physical (-23.7±14.9; t_{29}=-1.60, p=.12), and Role Function - Emotional (-14.1±9.6; t_{29}=-1.47, p=.15). Post-hoc comparisons revealed significant differences between Ctx+ and HC groups on General Health (-20.5±10.2; t_{29}=-2.0, p=.054), Physical Function (-47.1±15.8; t_{29}=-2.97, p=.006), Emotional Function (-24.6±8.3; t_{29}=-2.97, p=.001), Role Function - Physical (-24.5±13.7; t_{29}=-1.79, p=.084), Role Function - Emotional (-25.6±8.9; t_{29}=-2.88, p=.007), and Pain (-22.7±9.6; t_{29}=-2.36, p=.025). Post-hoc comparisons revealed significant differences between Ctx- and HC groups on General Health (-24.9±10.5; t_{29}=-2.4, p=.025) and Pain (-17.9±9.9; t_{29}=-1.81, p=.081).

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Marginally significant effects of age were only found in Social Function ($F_{(1,29)}$=2.22, p=.15). Effects of education were only found in Social Function ($F_{(1,29)}$=4.7, p=.038) and General Health ($F_{(1,29)}$=1.82, p=.19).

Neurocognitive

Nine outcome measures were obtained from neuropsychological assessments: 1) *Trails A* – processing speed, measured as completion time; 2) *Trails B* – processing speed and executive function, measured as completion time; 3) Stroop-W – word processing speed, measured as total number completed; 4) Stroop-C – color processing speed, measured as total number completed; 5) *Stroop-CW* – color processing speed and executive function, measured as total number completed; 6) *Stroop-I* – executive function, measured as difference between expected and observed Stroop-CW score; 7) *PASAT Attempts* – processing speed and divided attention, measured as total number attempted; 8) *PASAT Correct* – processing speed and divided attention, measured as total number correct; 9) *UFOV* – processing speed, divided attention, and selective attention, measured as processing time. Descriptive summaries of neurocognitive outcome measures are presented in

Table 3.

Of the 43 participants(Ctx+=14, Ctx-=14, HC=15) who completed baseline assessment, 1 Ctx+ patient could not complete Stroop-C or Stroop-CW due to colorblindness, 4 Ctx+ leukemia inpatients could not complete PASAT or UFOV, 1 Ctx- patient refused to complete PASAT, and 2 Ctx+ patients could not complete UFOV (assessed at different site, technical difficulties).

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Impaired Trails A performance was found in 7.1% of Ctx+ patients, 0% of Ctx- patients, and 6.7% of HC participants ($\chi^2_{(2)}$=1.6, p=.44). Impaired Trails B performance was found in 21.4% of Ctx+ patients, 7.1% of Ctx- patients, and 0% of HC participants ($\chi^2_{(2)}$=4.86, p=.088). Impaired Stroop-W performance was found in 14.3% of Ctx+ patients, 7.1% of Ctx- patients, and 6.7% of HC participants ($\chi^2_{(2)}$=.58, p=.75). Impaired Stroop-C performance was found in 21.4% of Ctx+ patients, 7.7% of Ctx- patients, and 6.7% of HC participants ($\chi^2_{(2)}$=1.71, p=.42). Impaired Stroop-CW performance was found in 21.4% of Ctx+ patients, 0% of Ctx- patients, and 0% of HC participants ($\chi^2_{(2)}$=7.07, p=.029). Impaired Stroop-I performance was found in 28.6% of Ctx+ patients, 15.4% of Ctx- patients, and 6.7% of HC participants ($\chi^2_{(2)}$=2.59, p=.27).

Marginally significant effects of group were found for Stroop-C ($F_{(2,36)}$=1.90, p=.16), Stroop-CW ($F_{(2,36)}$=2.73, p=.08), PASAT Attempts ($F_{(2,33)}$=2.56, p=.09), PASAT Correct ($F_{(2,33)}$=2.10, p=.14), and UFOV Subtest 3 ($F_{(2,32)}$=1.86, p=.17). Post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups on Stroop-C (-6.5±4.3; t_{36}=-1.51, p=.14), Stroop-CW (-7.0±4.6; t_{36}=-1.54, p=.13), and UFOV (76.6±43.2; t_{32}=1.77, p=.086). Post-hoc comparisons revealed significant differences between Ctx+ and HC groups on Stroop-C (-7.6±4.1; t_{36}=-1.83, p=.076), Stroop-CW (-10.1±4.4; t_{36}=-2.29, p=.028), PASAT Attempts (-6.4±2.8; t_{33}=-2.27, p=.03), PASAT Correct (-6.0±2.9; t_{33}=-2.04, p=.05), and UFOV (68.1±40.7; t_{32}=1.67, p=.10).

Significant effects of age were observed in Trails A ($F_{(1,37)}$=19.9, p<.0001), Trails B ($F_{(1,37)}$=5.87, p=.02), Stroop-C ($F_{(1,36)}$=19.05, p=.0001), Stroop-CW

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($F_{(1,36)}$=8.64, p=.006), and UFOV ($F_{(1,32)}$=9.97, p=.004). Marginally significant effects of age were observed for Stroop-I ($F_{(1,36)}$=1.90, p=.18). Significant effects of education were observed for Stroop-C ($F_{(1,36)}$=7.23, p=.011) and Trails A ($F_{(1,37)}$=3.25, p=.08).

Cognitive Electrophysiology

Capture Task Review. Six outcome measures were obtained from the Capture Task: 1) *Neutral RT* – processing speed, measured as response time during the Neutral condition; 2) *Singleton RT* – processing speed, measured as response time during the Singleton condition; 3) *Contingent RT* – processing speed, measured as response time during the Contingent condition; 4) *Singleton d'* – bottom-up attentional control, measured as difference in response times between Singleton and Neutral conditions; 5) *Contingent d'* – top-down attentional control, measured as difference in response times between Contingent and Neutral conditions; 6) *Contingent-to-Singleton d'* – attentional control, measured as difference in response times between Contingent and Singleton conditions.

Three outcome measures were obtained from EEG during the Capture Task: 1) *Singleton N2pc* – bottom-up attentional control, measured as N2pc amplitude during Singleton condition; 2) *Contingent N2pc* – top-down attentional control, measured as N2pc amplitude during Contingent condition; 3) *Contingent-to-Singleton N2pc* – attentional control, measured as difference in N2pc amplitude between Contingent and Singleton conditions.

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Filter Task Review. Six outcome measures were obtained from the Filter Task: 1) *Load-1 Accuracy* – working memory, measured as response accuracy during Load-1 condition; 2) *Load-3 Accuracy* – working memory, measured as response accuracy during Load-3 condition; 3) *Filter-1 Accuracy* – working memory, measured as response accuracy during Filter-1 condition; 4) *Filter-3 Accuracy* – working memory, measured as response accuracy during Filter-3 condition; 5) *Load-Dependent Accuracy* – working memory capacity, measured as difference in response accuracy between Load-3 and Load-1 conditions; 6) *Filter-Dependent Accuracy* – attentional control, measured as difference in response accuracy between Filter-1 and Load-1 conditions.

Six outcome measures were obtained from EEG during the Filter Task: 1) *Load-1 CDA* – storage load, measured as CDA amplitude during Load-1 condition; 2) *Load-3 CDA* – storage load, measured as CDA amplitude during Load-3 condition; 3) *Filter-1 CDA* – storage load, measured as CDA amplitude during Filter-1 condition; 4) *Filter-3 CDA* – storage load, measured as CDA amplitude during Filter-3 condition; 5) *Load-Dependent CDA* – storage load capacity, measured as difference in CDA amplitude between Load-3 and Load-1 conditions; 6) *Filter-Dependent CDA* – attentional control, measured as difference in CDA amplitude between Filter-1 and Load-1 conditions.

Of the 43 participants (Ctx+=14, Ctx-=14, HC=15) who completed baseline assessment, 5 Ctx+ patients could not complete cognitive electrophysiology because they were tested at a different location, 2 participants (1 Ctx-, 1 HC) refused to complete the Filter Task, 1 Ctx+ patient could not complete EEG

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recordings due to limited cap availability, and 1 Ctx- Filter Task EEG data set was lost due to technical complications. Descriptive summaries of quality of life outcome measures are presented in

Table 4.

Grand averaged electrophysiological waveforms are presented in

Figure 4. N2pc and CDA related activity are clearly shown during capture (

Figure 4A) and filter (

Figure 4B) tasks, respectively. Larger N2pc amplitudes were observed in the contingent cueing condition relative to the singleton cueing condition in the capture task, suggesting larger shifts of attention were made towards the task-relevant stimulus cue, thus replicating previous studies[308]. Larger CDA amplitudes were observed in the Load-3 condition relative to the Load-1 condition, suggesting larger storage-related neural activity was observed during larger memory loads and replicating previous studies[290]; furthermore, larger amplitudes were observed in the Filter-1 condition relative to the Load-1 condition, suggesting failures of filtering task-irrelevant memory items and replicating previous studies[210,301]. Thus, cognitive electrophysiological measures collected here replicated previous studies, confirming the validity of the experimental setup.

Capture Task. Marginally significant effects of group were found for Contingent RT ($F_{(2,33)}$=2.92, p=.07), Singleton d' ($F_{(2,33)}$=2.33, p=.11), Contingent d' (F=2.47, p=.10), Singleton N2pc ($F_{(2,32)}$=3.75, p=.03), and Contingent N2pc ($F_{(2,32)}$=2.64, p=.09). Post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups on Singleton d' (-.12±.06; t_{33}=-2.04, p=.049) and

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Contingent d' (-.14±.07; t_{33}=-1.93, p=.06). Post-hoc comparisons revealed significant differences between Ctx+ and HC groups on Contingent RT (-.11±.05; t_{33}=-2.38, p=.023), Contingent d' (-.14±.07; t_{33}=-2.05, p=.049), Singleton N2pc (-.56±.26; t_{32}=-2.42, p=.041), and Contingent N2pc (-.48±.29; t_{32}=-1.64, p=.11). Post-hoc comparisons revealed significant differences between Ctx- and HC groups on Contingent RT (-.06±.04; t_{33}=-1.34, p=.19), Singleton d' (.08±.05; t_{33}=1.59, p=.12), Singleton N2pc (-.55±.23; t_{32}=-2.42, p=.021), and Contingent N2pc (-.54±.26; t_{32}=-2.13, p=.041).

Significant effects of age were observed for Neutral RT ($F_{(1,33)}$=40.2, p<.0001), Singleton RT ($F_{(1,33)}$=38.98, p<.0001), and Contingent RT ($F_{(1,33)}$=42.26, p<.0001), Contingent N2pc ($F_{(1,32)}$=9.93, p=.04), and Contingent-to-Singleton N2pc ($F_{(1,32)}$=16.66, p=.0003). No effect of education was observed in any outcome measure.

Singleton N2pc amplitudes were significantly correlated with Neutral RT (r=.45, p=.006), Singleton RT (r=.43, p=.007), and Contingent RT (r=.45, p=.005) conditions. Contingent N2pc amplitudes were significantly correlated with Neutral RT (r=.63, p<.0001), Singleton RT (r=.61, p<.0001), and Contingent RT (r=.61, p<.0001), and Contingent d' (r=-.32, p=.057). Contingent-to-Singleton N2pc amplitudes were correlated with Neutral RT (r=.48, p=.0024), Singleton RT (r=.47, p=.003), and Contingent RT (r=.44, p=.006), Contingent d' (r=-.26, p=.12) and Contingent-to-Singleton d' (r=-.24, p=.15).

Filter Task. Marginally significant effects of group were found for response accuracy during the Load-3 condition ($F_{(2,31)}$=1.73, p=.19) and Load-Dependent

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Accuracy Costs ($F_{(2,31)}$=1.72, p=.20). Post-hoc comparisons revealed significant differences between Ctx+ and HC groups on Load-3 accuracy (-.08±.04; t_{31}=-1.86, p=.073) and Load-Dependent Accuracy Costs (.05±.03; t_{31}=1.72, p=.096), and differences between Ctx- and HC groups on Load-Dependent Accuracy Costs (.03±.03; t_{31}=1.36, p=.18). Marginally significant effects of age were found for response accuracy during Load-1 ($F_{(1,31)}$=2.58, p=.12), Load-3 ($F_{(1,31)}$=1.82, p=.19), and Filter-3 ($F_{(1,31)}$=2.06, p=.16) conditions, and CDA during Load-1 ($F_{(1,29)}$=1.71, p.20) and Filter-3 ($F_{(1,29)}$=1.81, p=.19) conditions.

CDA amplitudes in the Load-3 condition significantly correlated with response accuracy in the Load-1 (r=-.45, p=.007), Load-3 (r=-.51, p=.002), Filter-1 (r=-.45, p=.007), and Filter-3 (r=-.58, p=.0003) conditions, as well as Load-Dependent Accuracy Costs (r=.23, p=.19). CDA amplitudes in the Filter-3 condition significantly correlated with response accuracy in the Load-1 (r=-.32, p=.061), Load-3 (r=-.32, p=.061), Filter-1 (r=-2.3, p=.20), and Filter-3 (r=-.42, p=.01) conditions, as well as Filter-Dependent Accuracy Costs (r=-.27, p=.12). Load-dependent CDA amplitudes were associated with larger response accuracy in Load-1 (r=-.46, p=.006), Load-3 (r=-.41, p=.017), Filter-1 (r=-.45, p=.0075), and Filter-3 (r=-.48, p=.0042) conditions.

Cross-Platform Correlations

Quality of life measures were broadly associated with neurocognitive performance (Table 8). Quality of life measures were generally associated with Stroop-CW, Stroop-I, and PASAT performance, and Social Function and Role Function – Physical were associated with all three of these measures. Most

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quality of life measures were associated with d' measures from the Capture Task, and both Emotional Function and Social Function were associated with response accuracy and Load Accuracy in the Filter Task (Table 9). Most quality of life measures were associated with Load-3 CDA amplitudes from the Filter Task, and Social Function was associated with many outcome measures from the Filter Task (Table 10).

Neurocognitive measures were generally associated with by Load-3 accuracy in the Filter Task (Table 11). In the Capture Task, RT was associated with Trails A and Stroop-C performance, and d' measures were associated with Trails B, Stroop-C, and Stroop-CW performance. In the Filter Task, accuracy was associated with Trails A and B, Stroop-C, and PASAT performance; Load Accuracy was associated with Stroop-W performance; and Filter Accuracy was associated with Stroop-W and PASAT performance. Neural cognitive electrophysiology measures were generally associated with Stroop-CW and Stroop-I performance (Table 12).

A correlation matrix of Capture Task and Filter Task outcome measures is presented in Table 13. In general, Filter Task response accuracy was associated with Singleton d' and Cue N2pc amplitudes, and Filt-3 CDA amplitudes were associated with N2pc amplitudes.

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Longitudinal Assessment

Quality of Life

Generalized linear models were used to assess the omnibus effects of group and interact between group and visit on quality of life outcome measures. Model least square means are shown in

Table 5 and
Figure 5. A significant group by visit interaction was found for General Health ($F_{(4,48.1)}$=4.65, p=.003). Post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups at T3 (-15.8±11.3; $t_{41.3}$=-1.40, p=.17), between Ctx+ and HC groups at T1 (-17.2±10.4; $t_{37.6}$=-1.65, p=.11), T2 (-20.3±10.9; $t_{43.5}$=-1.87, p=.069), and T3 (-35.7±10.7; t_{41} = -3.33, p=.0018), and between Ctx- and HC groups at T1 (-26.6±10.7; $t_{37.4}$=-2.48, p=.018) and T3 (-19.9±10.9; $t_{39.2}$=-1.83, p=.075). In the Ctx+ group, significant reductions were observed when comparing T1-T3 (-18.4±4.7; $t_{47.6}$=-3.94, p=.0003) and T2-T3 (-15.6±5.0; $t_{45.9}$=-3.12, p=.0032) measurements; in the Ctx- group, significant increases were observed when comparing T1-T3 (6.8±4.4; $t_{46.8}$=1.56, p=.126)measurements.

Significant effects of group were found for General Health ($F_{(2,32.8)}$=3.82, p=.032), Physical Function ($F_{(2,31)}$=11.9, p=.0001), Emotional Function ($F_{(2,22)}$=7.41, p=.0035), Role Function – Emotional ($F_{(2,32.1)}$=4.29, p=.022), and Pain ($F_{(2,32.3)}$=5.76, p=.0073). No effect of age was found for any quality of life measure (p>.21). Post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups on Physical Function (-35.1±12.8; $t_{32.5}$=-2.75, p=.0097), Emotional Function (-16.4±6.3; $t_{23.4}$=-2.58, p=.017), and Role Function –

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Emotional (-12.3±9.2; $t_{32.8}$=-1.34, p=.19). Post-hoc comparisons revealed significant differences between Ctx+ and HC groups on Physical Function (-58.7±12.1; $t_{31.9}$=-4.87, p<.0001), Emotional Function (-22.7±6.0; t_{23}=-3.8, p=.0009), Role Function – Emotional (-25.4±8.7; $t_{32.4}$=-2.92, p=.006), and Pain (-25.6±8.1; $t_{32.6}$=-3.18, p=.0032). Post-hoc comparisons revealed significant differences between Ctx- and HC groups on Physical Function (-23.6±12.1; t_{29}=-1.96, p=.060), Role Function – Emotional (-13.1±8.8; $t_{31.1}$=-1.48, p=.15), and Pain (-20.6±8.2; $t_{31.5}$=-2.51, p=.0174).

Neurocognitive

Generalized linear models were used to assess the omnibus effects of group and interact between group and visit on neurocognitive performance. Model least square means are shown in

Table 6 and
Figure 6. Significant group by time interactions were found for performance on Trails B ($F_{(4,57.2)}$=1.96, p=.11), PASAT ($F_{(4,53.8)}$=2.77, p=.037), and UFOV ($F_{(4,60.8)}$=1.69, p=.16). Between-group post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups: (1) at T1 on Trails B (29.1±16.5; $t_{45.1}$=1.76, p=.084) and UFOV (74.5±34.2; $t_{75.8}$=2.98, p=.004) ; and (2) at T2 on PASAT (-4.7±3.2; $t_{40.7}$=-1.49, p=.143). Between-group post-hoc comparisons revealed significant differences between Ctx+ and HC groups: (1) at T1 on Trails B (28.1±16.2; $t_{45.1}$=1.73, p=.09), PASAT (-6.4±3.0; $t_{37.1}$=-2.16, p=.038), and UFOV (66.2±32.8; $t_{73.3}$=2.02, p=.047); (2) at T2 on PASAT (-7.3±3.0; t_{41}=-2.42, p=.02); and (3) at T3 on PASAT (-4.3±3.1; $t_{41.8}$=-1.41, p=.165). Between-group post-hoc comparisons revealed significant differences between Ctx- and HC

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groups at T3 on PASAT (-4.9±2.9; $t_{40.6}$=-1.68, p=.10). Within-group post-hoc comparisons revealed significant changes between T1-T2 measurements in: (1) the Ctx+ group on Trails B (-24.9±8.8; t_{58}=-2.81, p=.007) and UFOV (-85.7±31.4; $t_{58.4}$=-2.73, p=.0084); (2) the Ctx- group on PASAT (1.4±1.0; $t_{53.9}$=1.41, p=.16); (3) the HC group on UFOV (-33.3±24.6; $t_{60.2}$=-1.36, p=.18) and PASAT (1.3±.9; $t_{53.8}$=1.45, p=.15). Within-group post-hoc comparisons revealed significant changes between T1-T3 measurements in: (1) the Ctx+ group on Trails B (-28.9±9.3; t_{58}=-3.12, p=.003), UFOV (-95.6±32.8; $t_{60.2}$=-1.36, p=.18), and PASAT (3.9±1.2; $t_{53.9}$=3.2, p=.0023); (2) the Ctx- group on Trails B (-11.3±8.4; $t_{57.8}$=-1.34, p=.186); and (3) the HC group on UFOV (-35.6±25.3; $t_{61.1}$=-1.41, p=.16) and PASAT (1.8±1.0; $t_{53.9}$=1.89, p=.065). Within-group post-hoc comparisons revealed significant changes between T2-T3 measurements in: (1) the Ctx+ group on PASAT (3.5±1.4; $t_{53.9}$=2.61, p=.012); (2) the Ctx- group on Trails B (-14.0±8.5; $t_{55.7}$=-1.65, p=.105) and PASAT (-1.8±1.0; $t_{53.2}$=-1.69, p=.098); and (3) the HC group on Trails B (-10.3±8.0; $t_{55.9}$=-1.28, p=.20).

Significant effects of group were found for performance on Stroop-CW ($F_{(2,39)}$=4.24, p=.022) and Stroop-I ($F_{(2,39.1)}$=3.73, p=.033). Post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups on Stroop-CW (-6.6±3.8; $t_{40.2}$=-1.72, p=.093) and Stroop-I (4.8±3.1; $t_{40.6}$=1.56, p=.13). Post-hoc comparisons revealed significant differences between Ctx+ and HC groups on Stroop-CW (-10.6±3.7; $t_{38.8}$=2.90, p=.006) and Stroop-I (7.9±2.9; $t_{39.2}$=2.73, p=.0096).

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All neurocognitive measures showed significant effects of time (p<.16), demonstrating clear evidence for practice effects. Significant effects of age were observed in all neurocognitive measures (p<.02) except PASAT (p=.28). Significant effects of education were observed for Trails A ($F_{(1,36.3)}$=1.81, p=.19) and Stroop-C ($F_{(1,35.9)}$=8.41, p=.0063).

Cognitive Electrophysiology

Generalized linear models were used to assess the omnibus effects of group and interact between group and visit on cognitive electrophysiology outcome measures. Model least square means are shown in

Table 7 and
Figure 7. Significant effects of group were found for Singleton d' ($F_{(2,31.2)}$=2.17, p=.13), revealing significant differences between Ctx+ and Ctx- groups (-.10±.05; $t_{30.4}$=-2.08, p=.046). Significant interactions between group and visit were found for Contingent d' ($F_{(4,56.6)}$=1.55, p=.20), Singleton N2pc ($F_{(4,58.8)}$=1.74, p=.15) and Contingent N2pc ($F_{(4,56.7)}$=3.51, p=.012), Load-1 accuracy ($F_{(4,54.6)}$=2.65, p=.043), Load-3 accuracy ($F_{(4,56.6)}$=1.79, p=.14), and Filter-1 accuracy ($F_{(4,54.4)}$=3.14, p=.022), Filter-Dependent Accuracy Costs ($F_{(4,57.4)}$=1.54, p=.20), Load-1 CDA ($F_{(4,50.4)}$=2.70, p=.041), and Filter-Dependent CDA ($F_{(4,56.6)}$=1.79, p=.14). Between-group post-hoc comparisons revealed significant differences between Ctx+ and Ctx- groups: (1) at T1 for Contingent d' (-.15±.08; $t_{57.4}$=-1.86, p=.069); (2) at T2 for Filter-Dependent Accuracy Costs (-.03±.01; t_{84}=-2.53, p=.013), Load-1 CDA (-.3±.2; $t_{64.3}$=-1.39, p=.17), and Filter-Dependent CDA (.4±.2; $t_{76.6}$=1.00, p=.05); and (3) at T3 for Filter-Dependent CDA (-.3±.2; $t_{77.1}$=-1.39, p=.17). Between-group post-hoc comparisons revealed significant differences between

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Ctx+ and HC groups: (1) at T1 for Contingent d' (-.14±.08; $t_{58.8}$=-1.85, p=.069), Singleton N2pc (-.52±.3; $t_{72.5}$=-1.71, p=.091), Contingent N2pc (-.5±.4; $t_{59.3}$=-1.37, p=.18), and Filter-Dependent CDA (-.3±.2; $t_{76.8}$=-1.33, p=.19); (2) at T2 for Filter Accuracy (-.02±.01; t_{84}=-1.48, p=.14); and (3) at T3 for Contingent N2pc (.5±.4; $t_{63.7}$=1.49, p=.14) and Filter-Dependent CDA (-.3±.2; $t_{77.5}$=-1.37, p=.18). Between-group post-hoc comparisons revealed significant differences between Ctx- and HC groups: (1) at T1 for Singleton N2pc (-.5±.3; $t_{68.6}$=-1.93, p=.057) and Contingent N2pc (-.5±.3; $t_{55.4}$=-1.50, p=.14); (2) at T2 for Filter CDA (-.3±.2; $t_{76.7}$=-1.62, p=.11); and (3) at T3 for Contingent N2pc (.5±.3; $t_{55.4}$=-1.50, p=.15) and Load-1 CDA (-.4±.2; $t_{69.2}$=-1.8, p=.076). Post-hoc comparisons revealed significant within-group changes between T1-T2 measurements in: (1) the Ctx+ group for Contingent d' (.11±.06; $t_{54.9}$=1.72, p=.091), Contingent N2pc (.4±.3; $t_{55.9}$=1.57, p=.12), Load-1 Accuracy (.05±.02; t_{54}=2.57, p=.013), Load-3 Accuracy (.05±.02; t_{54}=2.57, p=.013), Load-1 CDA (-.3±.2; $t_{49.3}$=-1.77, p=.084), and Filter-Dependent CDA (-.3±.2; $t_{3.7}$=1.51, p=.14) measurements; and (2) in the HC group for Singleton N2pc (-.5±.2; $t_{60.1}$=-2.18, p=.033) and Contingent N2pc (-.4±.; t_{58}=-1.65, p=.10) measurements. Post-hoc comparisons revealed significant within-group changes between T1-T3 measurements in: (1) the Ctx+ group for Contingent N2pc (.4±.3; $t_{55.9}$=1.34, p=.18), and Load-3 Accuracy (.08±.02; t_{54}=3.96, p=.0002) measurements; (2) the Ctx- group for Contingent N2pc (.3±.2; $t_{58.2}$=1.29, p=.20) and Load-1 CDA (-.3±.2; $t_{53.6}$=-1.85, p=.07) measurements; and (3) the HC group for Contingent N2pc (-.7±.2; t_{58}=-2.97, p=.004) measurements.

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Post-hoc comparisons revealed significant within-group changes between T2-T3 measurements in: (1) the Ctx+ group for Load-1 Accuracy (.03±.02; $t_{54.4}$=1.33, p=.19), Filter Accuracy (.02±.01; $t_{58.7}$=1.50, p=.14), and Filter-Dependent CDA (-.6±.2; $t_{53.4}$=-2.52, p=.015) measurements; (2) the Ctx- group for Contingent N2pc (.4±.2; $t_{55.5}$=1.45, p=.15), Filter-Dependent Accuracy (-.02±.01; $t_{55.6}$=-1.96, p=.055), and Load-1 CDA measurements (-.5±.2; $t_{50.1}$=-2.82, p=.007); and (3) the HC group for Contingent d' (-.11±.06; $t_{56.4}$=-1.96, p=.055) measurements.

Significant effects of age were found for Neutral RT ($F_{(1,32.3)}$=44.18, p<.0001), Singleton RT ($F_{(1,32.5)}$=42.01, p<.0001), and Contingent RT ($F_{(1,32.3)}$=44.95, p<.0001), Contingent-to-Singleton d' ($F_{(1,32)}$=2.53, p=.12), Singleton N2pc ($F_{(1,32.6)}$=2.21, p=.15) and Contingent N2pc ($F_{(1,33.8)}$=7.64, p=.009), Load-3 accuracy ($F_{(1,29.4)}$=2.75, p=.11) and Filt-3 accuracy ($F_{(1,28.2)}$=2.42, p=.13), Load-1 CDA ($F_{(1,24.6)}$=3.26, p=.083), Load-3 CDA ($F_{(1,27.8)}$=15.76, p=.0005), and Filt-3 CDA ($F_{(1,29.2)}$=2.28, p=.14), and Load-Dependent CDA ($F_{(1,22.1)}$=12.63, p=.0018).

Comment on Modeling Outcomes

Multiple outcome measures were evaluated for evidence of chemotherapy-related changes. Distributional assumptions of outcome measures were confirmed by inspecting model residual plots, which revealed no detectable deviation from normality. To overcome potential limitations imposed by missing data, the same modeling procedures were run using data only from research participants that completed all three study visits. Comparing complete and reduced data sets, the same statistical omnibus pattern was observed for all

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outcome measures, with the exception of Trails B and Filter-Dependent Accuracy. For outcome measures replicating the omnibus pattern, all post-hoc contrasts replicated with the following exceptions: comparisons between Ctx+ and Ctx- groups at T2 for General Health and PASAT, and at T3 for General Health and Contingent N2pc; comparisons between Ctx+ and HC groups at T1 for Filter-Dependent CDA, and at T3 for PASAT; comparisons between T1-T2 in Ctx+ patients for General Health, and PASAT for Ctx- patients; and comparisons between T1-T3 for Filter-Dependent CDA. Differences observed in the reduced data set may reflect either a reduction in power or differences in patient characteristics for those patients who dropped out following T1 measurements. For example, study participants who dropped from the study were statistically less educated from those who remained in the study.

Discussion

Three primary patterns of results were observed across significant findings (Figure 9): 1) *Chemotherapy* effects – Ctx+ patients showed impairment after initiating chemotherapy; 2) *Cancer* effects – Ctx+ and Ctx- patients showed greater impairment than HC; 3) *Disease Severity* effects – Ctx+ patients showed greater impairment than Ctx- and HC groups. Of particular importance, a priori hypotheses predicted *Chemotherapy* effects across all outcome measures. Although results from some outcome measures were similar to one of the primary patterns, many outcome measures showed results that were consistent with more than one primary pattern. For example, some outcome measures

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showed evidence for both cancer and chemotherapy effects, in which both Ctx+ and Ctx- patients showed greater impairment than HC participants, and Ctx+ patients showed an additional increase in impairment that was not observed in Ctx- patients. Results are summarized according to these patterns.

Chemotherapy effects were noted when only Ctx+ patients showed declines in performance across consecutive study visits, suggestive of chemotherapy-specific changes. Chemotherapy effects were observed: 1) from T1-T2 in Filter-Dependent Accuracy and Contingent N2pc; and 2) from T2-T3 on Filter-Dependent CDA, Contingent N2pc, and General Health. Interestingly, these outcome measures were not predictive of each other.

Cancer effects were noted when both Ctx+ and Ctx- patients showed greater impairment than HC comparisons. Cancer effects were observed: 1) at each study visit in Role Function – Emotional, Physical Function, and Pain; 2) at T1 in Singleton N2pc, Contingent N2pc, and General Health; 3) at T2 in General Health; and 4) at T3 in PASAT. Of these measures, associations were only observed between Physical Function and PASAT performance.

Disease severity effects were noted when Ctx+ patients showed greater impairment than both Ctx- and HC groups at least during baseline assessment, suggestive of selective impairments in Ctx+ patients unexplained by chemotherapy treatment. Disease severity effects were observed: 1) at each study visit in Stroop, Physical Function, Role Function – Emotional, and Emotional Function; 2) at T1 in Trails B, UFOV, Contingent d', and Filter-Dependent CDA; and 3) at T2 in PASAT. In contrast to other effects, outcome

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measures showing disease severity effects were highly inter-related. Both Physical Function and Emotional Function were associated with Trails B, PASAT, and Contingent d'; Role Function – Emotional was associated with Stroop and Contingent d'; Trails B was associated with Contingent d', and Stroop was associated with Contingent d'.

In summary, Chemotherapy effects were observed in measures of attentional control; Cancer effects were observed in measures of attentional control and divided attention; and Disease Severity effects were observed in measures of executive function, selective attention, and attentional control.

Alternative explanations for study results should be considered. First, both cancer groups were prescribed medications known to affect brain and cognitive function, which may explain why cancer groups performed worse on neurocognitive measures across study visits. Second, Ctx+ patients were likely experiencing anxiety in anticipation of chemotherapy initiation; although anxiety measures were not collected here, anxiety may explain worse performance in Ctx+ patients during the first study visit, particularly in Trails B and UFOV measurements.

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CHAPTER 4: DRIVING SIMULATION RESULTS

(This chapter was reformatted from a manuscript submitted for publication in the Transportation Research Records: Journal of the Transportation Research Board)

Results

Study Enrollment

45 study participants were enrolled in the study at the time of analysis. Of enrolled participants, 17 participants did not complete driving simulator procedures due to the following reasons: simulator discomfort (n=4), dropped out prior to initiating study procedures (n=2), acute leukemia patients who could not be transported to driving simulator (n=4), technical difficulties with EEG (n=1), research assistant error (n=1), patient not wearing EEG during driving simulation (n=1), or ongoing study participation (n=4).

Of the 17 participants who did not perform the current study, 88% were HM patients (n=15) and 12% were HC participants (n=2). Of the 15 HM patients who did not perform the current study, 60% were receiving chemotherapy (n=9) and 40% were receiving best supportive care (n=6). Of the 4 participants with simulator adaptation syndrome, 50% were Ctx+ patients, 25% were Ctx- patients, and 25% were HC participants.

Study Patient Characteristics

One HM patient was excluded from analysis due to anisometropia, resulting in 14 HM patients and 13 HC comparisons that were included in the current study. HM patients were diagnosed with myelodysplastic syndrome (n=4), non-Hodgkin lymphoma (n=9), or multiple myeloma (n=1). Of the 14 HM patients

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that completed task procedures, 6 were receiving chemotherapy and 8 were receiving best supportive care. HM and HC groups did not differ along demographic dimensions of gender (*HM*: 50% female; *HC*: 46% female; χ^2=0.04, p=.84), age (*HM*: 61.6±14.0; *HC*: 58.0±17.0; t_{25}=.61, p=.55), or years of education (*HM*: 13.8±1.8; *HC*: 14.4±1.7; t_{25}=.90, p=.38).

Task Performance

Visual search performance was faster during baseline (989 ±302 milliseconds) compared to driving (1027 ±316 milliseconds) conditions (t_{26}=1.79, p=.08). HM and HC groups demonstrated comparable visual search performances in both baseline (HM=1055 ±380, HC=917 ±173; t_{25}=1.20, p=.24) and driving (HM=1105 ±386, HC=945 ±56; t_{25}=1.33, p=.20) conditions. Driving load-dependent differences in response times did not differ between HM (49 ±131 milliseconds) and HC (28 ±94 milliseconds) groups (t_{25}=.48, p=.64). Although between-group differences did not show evidence of statistical significance, odds of HM patients to show larger load-dependent differences in response times were 2.9 times the odds of HC patients.

Saccade Behavior

Previous EFRP studies have shown P1 amplitudes are more reliable following larger saccades [302]. Therefore, saccade events were submitted for analysis only if they fell within the amplitude range of 100-400 μV. HM and HC groups did not differ from each other in either total number of saccade events (*HM*: 148.4±97.1; *HC*: 158.1±111.4; t_{25}=.24, p=.81) or average saccade

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amplitude (*HM*: 179.0±16.8 μV; *HC*: 183.5±22.0 μV; t_{25}=.61, p=.55). These results are suggestive of similar saccadic behaviors between HM and HC groups.

EFRP

Grand-averaged EFRP waveforms for HM and HC groups are depicted in Figure 8A. Both groups demonstrated a clear positive deflection in EFRP amplitude in O1/O2 electrodes approximately 101 milliseconds after saccade offset consistent with P1 component. Average P1 amplitudes were larger for HC (2.51±1.60 μV) compared to HM (1.43±2.37 μV) groups (t_{25}=1.37, p=0.18; Cohen's d=0.54;
Figure 8C). Using a median-split of P1 amplitudes to partition individual drivers into high or low amplitude groups, odds of HM patients being in the low amplitude group were 4.1 (CI: 0.81-20.2) times to the odds of HC participants being in the low amplitude group. These results suggest the capacity of information processing following saccadic eye movements is reduced in HM patients compared to HC participants.

Slower response times during visual search tasks have important implications for detecting hazardous events. Next, we examined the relationship between post-saccadic information processing and behavioral costs sustained in visual search performance completed during driving relative to baseline performance. Using a median-split of response time differences, we noted different EFRP patterns between drivers showing low and high costs (

Figure 8B). During the P1 window, we observed larger amplitudes in the drivers sustaining smaller behavioral costs (r=-0.44, p=.022). P1 amplitudes were larger for the low-cost group (2.85±1.95 μV) compared to the high-cost group (1.11±1.87 μV; t_{25}=2.37, p=.03; Cohen's d=0.91). Indeed, odds of low-cost drivers showing larger P1 amplitudes were 20.2 (CI: 2.80-144.93; χ^2=10.8,

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p=.001) times the odds of high-cost drivers, suggesting lower P1 amplitudes may be associated with greater sensitivity to cognitive load on visual search behavior.

Next, we examined the relationship between behavioral costs and P1 amplitudes separately for HM and HC groups. We found that the odds of low-cost drivers showing larger P1 amplitudes were 31.9 (χ^2=6.64, p=.01) and 10.5 (χ^2=3.26, p=.07) times the odds of high-cost drivers in HM and HC groups, respectively. These results demonstrate post-saccade information processing capacity is similarly reduced across groups for drivers slower to detect targets within visual search displays.

Discussion

HM patients are at risk for impaired processing speed and attention [41,49,76], and impaired visual attention contributes to increased risk for vehicle crashes [196]. Consequently, this pilot study used state-of-the-art driving simulation and EEG to test the hypothesis that visual attention is impaired in cancer patients with HM. EFRP activity, an electrophysiological measure of information processing [309–312], showed promising evidence for reduced information processing in HM patients within 150 milliseconds of saccade termination. Amplitudes of the P1 EFRP component were reduced in HM compared to HC drivers. In contrast, HM and HC groups did not differ in saccade frequency or saccade magnitude. Thus, HM patients differed from HC comparisons in neural information processing and not in saccade measures.

We also found a relationship between driving load-dependent declines in visual search performance and P1 amplitudes (

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Figure 8B, D). Previous studies show that older drivers are slower to respond and use more eye movements during visual search within traffic scenes [313]. Patients with glaucoma, an age-related eye disease characterized by peripheral visual field loss, are slower to respond and deploy less efficient eye movements during visual search [314]. These behavioral patterns may reflect recruited auxiliary mechanisms to compensate for reduced information processing capacity in posterior cortex [101]. In the context of studies demonstrating age- and disease-related changes in visual search performance [313,314], increased saccade frequency may be an auxiliary mechanism for overcoming reduced neural information processing capacity by sampling driving scenes more frequently and consequently boosting signal-to-noise ratio. The current work shows reduced neural information processing capacity (i.e. P1 amplitudes) in drivers showing greater load-dependent declines in visual search performance, which was more prevalent in HM drivers. Our findings promote further investigations to elucidate the relationship between reduced neural information processing capacity and saccade behavior in HM patients during more complex visual search scenes.

We find that spatial loci of fixation and attentional resources are separable. This recalls the situation of inattentional blindness, [315,316] in which observers fail to detect an unexpected object within the locus of fixation (63, 65). These findings militate against exclusive reliance on eye-tracking methods to study visual attention. Further investigation is needed on relationships between disease-related changes in saccade behavior and information processing metrics in visual cortex. Combining eye-tracking and EFRP methods [317,318] promises to

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advance the understanding of how disease-related changes in attention translate to failures in hazard detection while driving.

We found no difference between HM and HC groups in visual search performance. One possible explanation is that our stimulus display promoted highly efficient visual search performance. Visual search efficiency has been shown to be affected by target and distractor similarity [319]. Displays comprised of low target-distractor similarity (e.g. red target, black distractors) and high distractor-distractor similarity (e.g. all black distractors) promote efficient, such that competing distractors fail to impose response time costs. Conversely, displays increasing in target-distractor similarity and decreasing in distractor-distractor similarity result in inefficient search, such that competing distractors impose response time costs that increase with distractor number. Thus, more complex visual search displays demand focused attention to discriminate between target and distractor search elements [293,296]. Here, our results indicate that performance is indistinguishable between cancer patients and healthy comparisons during efficient visual search. Future studies are needed to determine whether performance during visual search within complex displays is impaired in cancer patients.

EFRP measures can help probe how the brain processes information before, during, and after eye saccades. First, pre-saccadic shifts of attention enhance perceptual processing of locations and features present in the saccadic targets [320,321]. Second, saccadic suppression inhibits neural activity in low-level visual regions during eye movements [322–324]. Third, information processing is

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enhanced immediately following saccade offset [325,326]. Importantly, most of what we know about the neural mechanisms of visual attention during saccades has been gained through studies of non-human primates. EFRP studies in human subjects engaged in real-world relevant tasks may complement and advance our current understanding of visual attention mechanisms.

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GENERAL DISCUSSION

Results from this study provide several novel contributions to the state-of-the-science in chemotherapy-related cognitive impairment. First, behavioral correlates of attentional control were evaluated using cognitive tasks designed to probe specific attention functions. Second, neural correlates of attentional control were measured using EEG methods designed to dissect specific attention functions as they emerge in near-real time. Third, both behavioral and neural correlates of attentional control were evaluated in a real-world setting using simulations of naturalistic driving. As discussed below, these findings provide a foundation for better understanding the biological mechanisms of chemotherapy-related cognitive impairment. Although these findings represent important contributions to the field, several study limitations should be noted. Of particular importance, a complete interpretation of these results is constrained by the small sample size, heterogeneous cancer diagnoses and chemotherapy protocols, and missing data and patient drop out. Further large-scale confirmatory studies are therefore needed to fully appreciate the implications of these findings. Nevertheless, the following sections address initial study implications.

Contextualizing Study Results

Quality of life impairments have been demonstrated in hematological malignancy patients prior to treatment[33,46–49] and during treatment[47–49]. Here, cancer-related impairments in physical function, pain, and role function affected by emotional limitations were observed across study visits; chemotherapy-related reductions in general health were observed during treatment; and disease

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severity-related impairments in chemotherapy patients were noted across study visits. This study failed to replicate previous studies showing fatigue effects prior to and during treatment[47–49]. There are two possible reasons for this difference. Excluding factors contributing to study limitations, the most likely explanation is differences in fatigue assessments. Previous studies used either the EORTC[47,48] or BFI[49], whereas the current study used the SF-36. Critically, each of these measures differ in how far back in time patients are asked to assess their symptoms. SF-36 assess fatigue symptoms over the past 4 weeks, whereas the BFI[327] and the EORTC[328] assess fatigue symptoms over the past 24 hours and the past week, respectively. Thus, differences in the timescale of assessment most likely explains differences between the current and previous studies on fatigue assessments. Nevertheless, the current study largely replicates previous quality of life studies of hematological malignancy patients.

Cognitive impairments have been noted in hematological malignancy patients prior to treatment[49,70] and during treatment[49,55,70]. These studies found impairments primarily in the domains of memory[49,55], executive function[49,55], and processing speed[49]. Here, cognitive performance was impaired in the domains of executive function (Stroop-CW, Stroop-I) and working memory (PASAT) both prior to and during chemotherapy. The current study therefore replicates previous studies showing impaired executive function prior to and during treatment. In contrast, this study failed to replicate previous studies showing pre-treatment impairments in Trails A[49]. The study sample demonstrating pre-treatment effects on Trails A was comprised of 65% MDS and 35% AML patients.

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In the current study, the chemotherapy group was comprised of only 7% MDS and 20% AML patients. Differences in patient diagnoses is most likely explanation for these differences, though further study is required to evaluate disease-specific differences in pre-treatment cognitive impairment in hematological malignancies.

To date, only cross-sectional studies have examined differences in neural function in hematological malignancy. These studies demonstrated reliable differences between chemotherapy and non-chemotherapy groups in PET activity within the dorsal-attention and central-executive networks[52,96]. One study showed that PET activity in these networks correlated negatively with number of chemotherapy cycles and positively with time since chemotherapy, suggesting chemotherapy patients experience acute impairment followed by recovery of normal brain metabolism following treatment[52]. Another study demonstrated distinguishable multivariate patterns of network activity between chemotherapy and non-chemotherapy groups, suggesting chemotherapy functionally alters network activity differently from cancer-related effects[96]. In the current study, cognitive functions governed by dorsal attention and central executive networks were examined using N2pc and CDA amplitudes, respectively. Prior to treatment, neural activity showed cancer-related impairments in both N2pc and CDA activity. During treatment, neural activity showed: (1) both cancer- and chemotherapy-related changes in N2pc amplitudes; and (2) chemotherapy-related changes only in CDA amplitudes.

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Results shown in the current work replicates and extends previous cross-sectional studies in three major ways. First, this study examined electrophysiological measures of attention and executive functions prior to and following treatment, providing a longitudinal assessment of associated chemotherapy-related changes in a novel neural measure. These findings confirmed cancer- and chemotherapy-related changes in neural measures of attention and executive function. Second, this study confirmed previous study results showing patterns of PET activity in central executive network that were dissociable chemotherapy patients and comparisons[52,96]. Here, CDA amplitudes were affected differently in chemotherapy and non-chemotherapy cancer patients, which were both different from healthy comparisons. Third, this study confirmed previous study results showing different trends in patterns of PET activity within the dorsal attention network[96]. Here, we showed N2pc amplitudes differed between chemotherapy patients and comparison groups, though not in a predictable way. Thus, further work is required to better understand how dorsal attention network properties change with chemotherapy, and how dorsal attention and central executive network properties change and interact with cancer and chemotherapy.

This study is the first to evaluate how cognitive impairment in cancer patients maps onto real-world task demands studied in high-fidelity simulated driving settings. We used driving simulation, eye movement, and EEG measures to study visual attention and driving in cancer patients with HM. Lower EFRP activity following saccade offset was observed in drivers showing greater

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impairment in visual search performance while driving, consistent with previous studies showing EFRP activity is associated with task performance. We found similarly reduced EFRP activity in drivers diagnosed with a HM. In contrast, measures of saccade behavior such as frequency and magnitude were unrelated to both cognitive function and disease status. These results support a functional dissociation between saccade behavior and post-saccade information processing during driving and may serve as a neural measure of impaired information processing in diseased and cognitively impaired populations. These findings are particularly important for future work, given the relationship between impaired visual attention and increased risk for vehicle crashes [196]. Furthermore, these results confirm that an increased risk for impaired processing speed and attention in hematological malignancy patients[41,49,76] translates to impaired processing capacity in a real-world driving setting.

Comparison to Other Cancer Populations

In comparison to the limited studies of chemotherapy-related cognitive impairment in hematological malignancies, numerous studies have been conducted in other cancer populations. For the purposes of comparison to the current study, only those studies with a longitudinal design and comparison groups are reviewed here[170–172,174,175,177,183–187,189,329–331]. Prior to treatment, behavioral studies demonstrated cancer-related impairments in processing speed[170–172,330,331], working memory[171,330,331], and verbal memory[174,330,331]; functional MRI studies have shown cancer-related differences in cortical activity within frontal and parietal regions[187], as well as greater spatial variance within the

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executive function network[175,177]. Up to 3-months following treatment, previous behavioral studies have demonstrated chemotherapy-related impairments in processing speed[183,184,329], working memory[183], executive function[171,183,184], and verbal memory[171]; structural MRI studies have shown chemotherapy-related reductions in gray matter volume within frontal[184186189], parietal[184189], and temporal[184186189] cortical regions; functional MRI studies have shown chemotherapy-related changes in task-based cortical activity within frontal, parietal, and temporal regions[187]. Askren and colleagues[175] studied network-level activity in breast cancer patients, and found no difference in spatial variance within the executive function network despite finding baseline differences between groups prior to treatment. These results are similar to the pattern observed in the filter CDA effects reported here, in which Ctx+ and Ctx- groups demonstrated larger CDA effects prior to treatment, but then Ctx+ patients showed a reduction in CDA effect at one-month followed by an increase in CDA effect at three-months. Whether this pattern reflects underlying chemotherapy-related changes in executive function network activity demands further study.

Results shown in the current work replicate and extend studies performed in other cancer populations in several important ways. First, this work contributes to a growing body of literature demonstrating cancer- and chemotherapy-related cognitive impairment in hematological malignancies, an understudied cancer population. Second, this work examined neural correlates of cognitive function in a longitudinal study design, which is lacking in studies of hematological malignancy; in contrast, breast cancer studies in particular have focused on

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longitudinal designs with appropriate comparison groups to elucidate the roles of tumor biology and chemotherapy toxicity in cognitive impairment observed in cancer patients. Third, cognitive and neural measures examined here recruit frontal and parietal cortical regions that have shown both structural and functional changes in other cancer populations, suggesting overlapping mechanisms. Fourth, this work used an experimental study design to evaluate potential changes in driving performance, a critical activity of daily living. Finding evidence for the potential impact of chemotherapy on information processing capacity and on-road hazard detection demands further studies into whether cancer patients may be public health and safety concern that demands mitigation through novel intervention and technology development.

Attentional Control Mechanisms

In this section, basic research on attentional control and its underlying neurophysiological and neurochemical mechanisms are reviewed. Once the theoretical framework for attentional control mechanisms is established, I transition in the next section (*Biological Mechanisms of Cognitive Impairment*) to contextualizing putative biological mechanisms of cancer- and chemotherapy-related cognitive impairment within the framework of attentional control mechanisms. Together, these sections motivate future research into specific interactions between tumor biology, treatment toxicity, and attentional control mechanisms.

Attentional control broadly refers to the ability to efficiently and effectively execute basic attention processes during complex cognitive tasks. Four basic

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attention processes are traditionally distinguished: (1) focusing limited-capacity attentional resources on most relevant information[332]; (2) selecting information to be focused on by biasing attention toward relevant information among competing irrelevant information[192]; (3) improving the quality of selected information by facilitating sensory processing of information-specific neural activity[333,334]; and (4) sustaining attentional resources over selected information or potential sources of information[335–337]. Attention processes can be deployed towards information externally (i.e. in the environment) or internally (i.e. in mind) present with respect to the observer[193,194]. Thus, attentional control must effectively manage a limited pool of resources by selecting and enhancing the processing of only most relevant information over a sustained period of time.

Attentional control coordinates attention processes through competitive interactions between dorsal and ventral attention networks. Dorsal attention networks are involved in disengagement of attention from and orienting of attention toward information[179,202], and are primarily distributed along frontal and parietal cortical regions including: superior frontal gyrus (SFG), medial frontal gyrus (MFG), intraparietal sulcus (IPS), lateral occipital gyrus (LOG), superior temporal sulcus (STS), and posterior cingulate (PC)[179]. Ventral attention networks are involved in selectively modulating information-specific neural activity in sensory cortex[179], and are primarily distributed along occipital and parietal cortical regions including: inferior frontal gyrus (SFG), precentral gyrus (preCG), postcentral gyrus (postCG), superior parietal lobule (SPL), and cuneus[179]. Cortical regions distributed across dorsal and ventral attention

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networks show both structural and functional dissociation based on measures of white matter tractography[338] and resting-state fMRI[339,340]. Thus, dorsal and ventral attention networks demonstrate putative roles for information selection and enhancement, respectively.

Orienting of attention results primarily from bi-directional patterns of front-parietal neural activity within the dorsal stream[202,341–344]: (1) voluntary control through top-down frontal-to-parietal modulation[344,345]; or (2) involuntary control through bottom-up parietal-to-frontal modulation[344]. Top-down modulation selectively increases the magnitude of signal available in population-level neural activity specific to the attended information[346–350], effectively communicating greater neural activity associated with relevant information at the expense of irrelevant information[351,352]. Theoretical models propose that information-specific activity is better communicated within and between cortical regions by selective rhythmic synchronization of neuronal activity coding for relevant information[204,353,354]. Voluntary control of attention is disrupted when a salient stimulus (e.g. car horn) captures attention, resulting in an involuntary response to the novel stimulus[355–358]. Bottom-up modulation effectively increases the magnitude of neural activity associated with the salient stimulus in sensory cortex[359], which is amplified in parietal cortex[360,361] and subsequently propagated to frontal cortex[362,363]. Theoretical models propose that patterns of neural activity coding for information-specific features and spatial locations represent distinct cortical processes[364,365]. Thus, where and what attention is directed towards depends on interactions between voluntary and involuntary control mechanisms.

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Competitive interactions between dorsal and ventral attention networks collectively determine the locus of spatial attention and the quality of attended information[296,366–368]. Although the dorsal attention network activates top-down control over the ventral attention network to select and enhance goal-relevant neural activity, salient or unexpected information engage the ventral attention network and activate bottom-up control over the dorsal attention network to orient attention to the salient information[369–372]. Furthermore, bottom-up control over the dorsal attention network is more likely to occur when the salient information is relevant to goals of the observer (e.g. hearing a car horn while either driving or watching a movie) [286,289]. Conversely, information processing in regions activated by bottom-up control is inhibited following the salient stimulus[373], reflecting disengagement of dorsal attention network from bottom-up control and subsequent suppression of activated regions within the ventral attention network.

Attentional control mechanisms are also critical to eye movements (or saccades) [374]. According to this model, the same network of brain areas are activated for saccades and spatial attention[342,375,376], which coordinate to shift spatial attention prior to saccades. Numerous studies suggest that frontal eye fields (FEF), superior colliculus (SC), and substantia nigra are integral to coordinating spatial attention and saccades[377–380]. Prior to saccades, spatial attention disengages from the current location, orients to a new location, and selectively modulates the new target of attention[98]. Supporting this hypothesis, neural activity is biased towards saccade targets prior to initiating the saccade[203,381–384], and target detection and discrimination is better at saccade

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terminations[385,386]. Thus, attentional control is critical to attention processes within and between eye fixations.

Long-range communication of information-specific neural activity within and between dorsal and ventral attention networks depends on neurotransmitter systems to propagate action potentials across the synaptic cleft. Neuromodulation of dorsal and ventral attention networks has been well-documented in dopaminergic and serotonergic neurotransmitter systems. Dorsal attention network prefrontal cortex (PFC) receives afferent connections from dopaminergic neurons within the ventral tegmental area and substantia nigra pars compacta[387–389]. PFC activity is modulated by multiple receptor subtypes[389,390], including dopamine receptor 2 (D2R) which has been associated with cognitive flexibility and decision making[213,215,391–393]. PFC dopaminergic activity is associated with selective attention[394–396] and working memory storage[214,397–401], as well as facilitating top-down modulation of neural activity in early visual cortex[395]. Theoretical models propose that dopaminergic systems are involved in inhibitory control over bottom-up control over dorsal attention network by spatially tuning neuronal signals[402–404], enhancing signal-to-noise ratios and suppressing competing information[211,405,406]. Polymorphisms in the catechol-O-methyltransferase (COMT) gene, which regulate dopamine activation in PFC[407–409], have been associated with attentional control. COMT knockout mice show increased dopamine levels[409,410]. In humans, polymorphic differences have been associated with better attentional control performance and stronger neurophysiological responses in cingulate cortex[212]. PFC also receives afferent

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connections from serotonergic neurons within the raphe nuclei[411], and PFC activity is modulated by a dense distribution of serotonin receptors[412]. PFC serotonergic activity has been associated with executive functions[413] and cognitive flexibility[414]. Polymorphisms in the serotonin transporter-linked polymorphic region (5-HTTLPR) gene, which regulate serotonin receptor density and neurotransmitter availability, have specifically been associated with attentional control[216,218,415]. In rat models, homozygous 5-HTTLPR knockout rats showed improved inhibitory control, whereas heterozygous knockout rats were similar to wild type rats[216]. In humans, polymorphic differences have been associated with better inhibitory control[415] and working memory[415] performance, and have shown differential effects on event-related potential measures associated with task performance[218,415].

An emerging field of research is investigating the impact of peripheral inflammation on complex cognitive functions governed at the molecular level, including synaptic plasticity, neurogenesis, and neuromodulation[416,417]. Conceptualized as “sickness behavior,” peripheral inflammation emerges from immune-mediated reorganization of homeostatic and behavioral priorities[418,419]. Increases in peripheral pro-inflammatory cytokine proteins likely activates a distributed network of brain cells that express cytokines and cytokine receptors[418]. Supporting this hypothesis, studies have demonstrated relationship between induced inflammatory responses and changes in cognitive function[220–223,420–422]. Specifically, these studies have identified IL-6[221,223,420–422], TNF-α[222], and IL-8[223] in mediating inflammation-related cognitive changes. Vaccine-

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induced peripheral inflammation is associated with altered substantia nigra activity[221], which is associated with dopaminergic neurotransmitter system and dorsal attention network, and compensatory recruitment of dorsolateral PFC and anterior cingulate cortex. Critically, induced inflammatory responses were not associated with changes in cortisol levels[223], potentially ruling out the contributing of psychosocial stress to inflammation-mediated cognitive changes. Thus, peripheral inflammatory activity may interact with dopaminergic neurotransmitter systems, resulting in altered attentional control function within the dorsal attention network.

Biological Mechanisms of Cognitive Impairment

Understanding the underlying biological mechanisms of cancer- and chemotherapy-related cognitive impairment is critical to developing interventions and treatments for prevention and control efforts. Current models propose that cancer- and chemotherapy-related cognitive impairment is initiated by peripheral inflammation[167]. Here, hematological malignancy patients, receiving either chemotherapy or best supportive care, showed characteristically different longitudinal outcomes than healthy comparisons in electrophysiological measures of attentional control (i.e. N2pc and CDA amplitudes). These results suggest tumor biology and chemotherapy toxicity may affect downstream processes that specifically disrupts neural mechanisms of attentional control. To elucidate this putative mechanism, it is critical to demonstrate that peripheral inflammation induces a biochemical pathway that leads to the disruption of: (1) cortical structures within dorsal and ventral attention networks underlying

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attentional control functions; (2) functional connectivity between cortical structures within attentional control networks; (3) neurotransmitter systems that modulate activity within attentional control networks; and (4) top-down and bottom-up control processes central to attentional control functions (Figure 1). In the following sections, patterns of results from both animal and human studies are presented to support evidence for this pathway.

Rodent models have shown evidence for a signaling cascade bridging systemic and neuro-inflammatory pathways[423], providing a putative mechanism for peripheral inflammation to induce changes to neural structure and function. Current evidence suggests this periphery-to-brain pathway is mediated by NF-κB activity[424–426], which degrades the integrity of the blood-brain barrier[427–430], subsequently facilitating activation of cytokines produced by microglia and astrocytes[431]. In rodents, increases in circulating levels of the pro-inflammatory cytokine interleukin-6 (IL-6) have been associated with increases in hippocampal concentrations of IL-6[432–434], IL-1b[433], and TNF-α[432,434]. Furthermore, systemic injections of chemotherapeutic treatments for hematological malignancies, including cyclophosphamide, bortezomib, and methotrexate, have been associated with increases in pro-inflammatory cytokines in neural tissue[131,139–141]. These studies support the hypothesis that system inflammation induces microglial activation and subsequent neuroinflammatory pathways.

Rodent models have also shown evidence for a relationship between microglial activation and biochemical functions underlying cortical structure and function. Systemic injections of chemotherapeutic treatments for hematological

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malignancies have been associated with neuronal degeneration[113,114,122,123,125] and apoptosis[112,116,126,128,129], which is likely due to decreases in bone-derived neurotrophic factors (BDNF) observed in the same treatments [114,134]. According to the inflammation-dopamine hypothesis, pro-inflammatory cytokines can alter neurotransmitter receptors[191,419,435,436] and signaling[435,436]. Supporting this hypothesis, systemic treatment with chemotherapy has been associated with decreases in concentrations of glutamate[130,132,133,135,437–444], dopamine[136,137,434], and serotonin[138,434,445]. Importantly, these neurotransmitters have been associated with attentional control functions in both rodents and humans.

Although no direct translational links have been established between chemotherapy-related inflammation-mediated neurotransmitter dysfunction and attentional control dysfunction in cancer patients, current data supports this link. In humans, dopaminergic and serotonergic neurotransmitter systems have been associated with functional activity within the dorsal and ventral attention networks. Likewise, cancer- and chemotherapy-related changes in cortical structure and function have been demonstrated in dorsal and ventral attention networks. Specific regions impaired within the dorsal attention network include: SFG[52,189,446–449], MFG[52,96,175,177,184,186,187,189,446–451], IPS[96,175,177,187,446,447,449], STG[96,184,189,447,448], LOG[446,447,450], postCing[446]; specific regions impaired within the ventral attention network include: SMA/Cingulate[52,96,175,177,184,186,450,451], preCG[96,184,187,189,448,450], postCG[96,184,447,449,451], SPL[96,184,187,446,447,449], CUN[96,447], IFG[96,175,177,184,186,187,446–448,451], LG/FG[446]. These results indicate potential to find a

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relationship between inflammation-mediated neurotransmitter dysfunction and attentional control network dysfunction in human cancer studies.

Together, this translational research program requires further study to elucidate the link between peripheral inflammation and attentional control impairment in both human and non-human models. In rodent models, future studies should develop neuroimaging tools to study cortical networks involved in attentional control; in particular, cognitive electrophysiology measures similar to what was developed here would allow further study of task-related neural activity. In human models, future studies should incorporate methodologies that measure neurotransmitter concentrations and function; in particular, imaging modalities such as magnetic resonance spectroscopy (MRS) would allow imaging of neurotransmitter concentrations in dorsal and ventral attention networks. Furthermore, previous studies reviewed here should be replicated in addition to appending these proposed measures into study protocols to confirm and extend findings.

Limitations of Current Study

This study was limited by a small sample size, due primarily to the experimental nature of the design. Study group sample sizes (n=15) were chosen to collect pilot data to determine the feasibility of study methods and obtain descriptive statistics to conduct power analysis to inform future large-scale confirmatory studies. This study was successful in both regards: I successfully collected proposed data from all three study groups, demonstrating study feasibility, and I was able to identify several key measures that hold promise for

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future large-scale confirmatory analyses. Furthermore, I obtained important attrition data across groups, allowing for appropriate sample size adjustments across groups to increase the likelihood of achieving sufficient power in larger studies. Thus, although initially small sample sizes were further reduced by patient dropout, the study goals were achieved by obtaining important outcome measure and attrition data.

Multiple hematological malignancies were studied here. In conjunction with the small sample size noted above, I was unable to evaluate potential effects of cancer pathophysiology on outcome measures. Although differences in cognitive function across groups are foreseeable, given differences in hematopoietic lineages affected and tumor microenvironments, this question remains unexplored and in need of further study. Future large-scale studies may focus on a single sub-type of hematological malignancy or include cancer diagnosis as a model factor. Studies implementing the former strategy would be limited by small sample sizes, but would have a more pure disease-specific sample; studies implementing the latter strategy would be more successful in recruiting large sample sizes, but would have to rely on appropriate modeling procedures to separate disease-specific factors. Similar to the problem of enrolling multiple hematological malignancies, multiple chemotherapy protocols and agents were used in the chemotherapy group. This limitation precludes evaluating chemotherapy agent-specific effects on outcome measures presented here. Thus, future studies would benefit from more controlled studies of cancer- and chemotherapy-related effects.

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Along similar lines, an important goal for future studies in the literature, including the current dissertation research, would be to determine how different cancer types across solid and liquid malignancies – and their interaction with chemotherapy agents – affects cognitive function. One important distinction between cancer pathophysiology is the emergence of the tumor microenvironment, in particular the positive feedback loop induced by the inflammation-mediated immune response. For example, inflammation is generally more pronounced in earlier stages of liquid tumors compared to solid tumors, whereas chemotherapy-induced changes in inflammation are more pronounced in solid tumors than in liquid tumors. Understanding the relationship between cancer type, chemotherapy toxicity, inflammation, and cognitive impairment is critical to mapping out associated changes in activities of daily living.

Due to patient characteristics, time constraints, and technical difficulties, completion rates of the driving simulation study were lower than data collection elements from other measures. As a result, these data were assessed using an analytic routine that differed from the rest of the study. Thus, this study was unable to evaluate separable effects of cancer and chemotherapy on electrophysiological and driving performance outcomes. Nevertheless, I obtained useful data that demonstrated marginally significant effects of cancer status on behavioral and electrophysiological measures of information processing capacity. In designing future studies, time limitations of the patient should be taken into consideration so that driving simulation studies are more complete. This

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proposed change would result in one of two future directions: (1) reduce the number of cognitive and electrophysiological measures to allow for more time to complete driving simulation; or (2) conduct separate driving simulation studies that can focus more on driving performance measures and outcomes. In the former case, these studies would be well-suited to develop translational research programs aimed at understanding the relationship between cancer- and chemotherapy-related cognitive changes and driving performance – an instrumental activity of daily living; in the latter case, these studies would be well-suited for extending these pilot findings into future driving studies that utilize on-road technologies to record driving performance in the wild and monitor cancer- and chemotherapy-related changes in the prevalence of real-world hazardous events.

This study did not include a subjective measure of cognitive performance. Current evidence is controversial regarding the relationship between subjective and object assessments of cognitive performance. While some studies have found that complaints of cognitive dysfunction are accompanied with impairments in objective cognitive performance, other studies have failed to observe this relationship, instead finding that subjective cognitive function is better predicted by psychosocial status. Thus, this study was unable to contribute to this growing debate regarding the external validity of cross-platform tools.

Changes in electrophysiological biomarkers of attentional control function across study groups and assessments failed to match a priori predictions, resulting in a failure to accept both the null hypothesis and alternative hypothesis.

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Nevertheless, these effects continue to support cancer- and chemotherapy-related changes in attentional control function. Without MRI measures to map out concurrent changes in cortical structure and function, it is difficult to contextualize these unpredicted changes within the theoretical framework of attentional control network activity. Future studies should include MRI measures to better understand how cancer- and chemotherapy-related changes may be related to changes in attentional control network activity.

Conclusions

A growing body of literature suggests cancer patients are susceptible to cognitive impairment due to factors related to tumor biology and chemotherapy toxicity, in addition to concurrent demographic and psychosocial factors that affect quality of life. This dissertation research sought to better understand the neural mechanisms of cancer- and chemotherapy-related cognitive impairment by developing an cognitive electrophysiology toolbox designed to dissect core attentional control functions that may explain broad patterns of cognitive impairment. These tools, which included laboratory implemented computer-based experimental psychology tasks and driving simulations, were implemented in a longitudinal study design that investigated recently diagnosed hematological malignancy patients prior to starting chemotherapy, and following one-month and three-months of chemotherapy. Comparison groups included hematological malignancy patients receiving best support care or no treatment, and demographically-matched healthy controls. Reliable changes were noted in across laboratory measures, providing novel behavioral and neural evidence for

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cancer- and chemotherapy-related impairments in attentional control function, and a promising translational research program for investigating the impact of attentional control dysfunction on simulated driving performance. Furthermore, laboratory measures correlated with performance on neuropsychological tests selected to probe similar attentional control functions.

There are several opportunities for future study. First, a large-scale confirmatory study is necessary to prove out the pattern of findings shown here. Second, additional neuroimaging methodologies (e.g. MRI) is needed to identify how electrophysiological patterns reported here are related to pathology in cortical structure and function. For example, cognitive aging literature suggests a posterior-to-anterior shift in neural activity is a hallmark of the aging brain; in future studies, it is important to determine whether similar shifts in cancer- and chemotherapy-related cognitive impairment contributes to changes in electrophysiological patterns shown here. Third, mechanisms of impairment in attentional control function should be proved out to identify key prevention and intervention strategies. As discussed in the Biological Mechanisms section, leading theories suggest peripheral inflammation induced by tumor biology and chemotherapy toxicity activates a signaling cascade, resulting in neuroinflammatory responses that affect neuronal signaling and structural integrity. Biomarkers for these biochemical processes should be incorporated into future human studies, and electrophysiological measures should to be developed for future animal studies to bridge this translational gap. Finally, the relationship between cognitive impairment and driving performance in cancer

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patients is entirely unexplored. Future studies should focus on developing research programs aimed at identifying driving behaviors that are particularly sensitive to changes in attentional control function.

In conclusion, this dissertation research offers a key theoretical contribution to the underlying cognitive and neural mechanisms of cancer- and chemotherapy-related cognitive impairment. Paradigms developed here provide a platform for better understanding the relationship between chemotherapy-induced neurotoxicity reported in animal studies and patterns of cognitive impairment reported in human studies. As cancer survivor populations continue to grow with improving treatment outcomes, it is critical to ensure the long-term quality of life of these patients. Addressing the underlying impairments in attentional control function reported here promises to achieve this goal.

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TABLES

CHARACTERISTIC	CTX+	CTX-	HC
Demographics			
Age	59.3 (15.2)	63.2 (10.9)	60.0 (16.5)
Gender (Males)	8 (53%)	6 (40%)	7 (47%)
Education (Years)	13.9 (1.7)	13.5 (1.3)	14.3 (1.6)
Handedness (% Right*)*	11 (85%)	13 (93%)	12 (80%)
Race (White)	15 (100%)	14 (93%)	15 (100%)
Marital Status (Married)	11 (73%)	10 (67%)	8 (53%)
General Function			
MMSE	29.5 (.7)	29.0 (1.4)	29.3 (1.6)
Vision (% Normal)	5 (36%)	5 (36%)	4 (29%)
Diagnosis			
NHL	10 (67%)	6 (40%)	
MDS	1 (7%)	6 (40%)	
AML	3 (20%)	-	
CLL	-	2 (13%)	
ALL	1 (7%)	-	
MM	-	1 (7%)	

Table 1. Patient Characteristics.

Continuous data are presented as means and standard deviations: M (SD); Categorical data are presented as frequencies and percentatges: N (%). (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group; MMSE = Mini-Mental Status Examination; NHL = non-Hodgkin lymphoma; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; CLL=chronic lymphocytic leukemia; ALL = acute lymphoblastic leukemia; MM = multiple myeloma).

BASELINE QUALITY OF LIFE

Measure	*Ctx+*	*Ctx-*	*HC*
SF-36	N=10	N=10	N=14
Gen Health	67.5±28.0	61.0±33.7	89.6±12.0
Physical F	35.0±37.6	70.0±43.8	82.1±31.7
Emotion F	62.5±30.0	75.0±19.5	87.5±4.9
Social F	57.8±32.4	66.0±29.4	79.3±19.2
Physical R	63.3±42.9	86.7±32.2	88.1±21.1
Emotion R	39.2±24.4	52.5±23.5	65.4±15.2
Fatigue	78.0±11.7	83.2±9.8	82.3±13.7
Pain	51.0±27.9	55.5±20.2	73.9±19.1

Table 2. Baseline Quality of Life.

Means ± standard deviations for raw quality of life data. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group).

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BASELINE NEUROCOGNITIVE PERFORMANCE

Measure	*Ctx+*	*Ctx-*	*HC*
TMT	N=14	N=14	N=15
TMT-A	31.9±14.6	27.6±8.4	28.5±11.5
TMT-B	95.4±78.8	68.6±20.2	69.0±38.3
STROOP	N=14	N=14	N=15
Stroop-W	91.4±13.4	91.0±12.4	95.5±17.5
Stroop-C	64.1±12.9	71.7±14.6	71.5±13.7
Stroop-CW	27.7±12.6	34.0±10.5	37.1±14.0
Stroop-I	9.7±10.5	5.8±10.9	3.6±11.4
PASAT	N=10	N=13	N=15
Attempted	20.3±6.8	24.0±4.8	26.6±8.1
Correct	17.9±7.1	21.6±5.3	23.9±8.5
UFOV	N=9	N=13	N=15
Subtest 3	190.3±132.2	123.7±68.7	129.9±117.9

Table 3. Baseline Neurocognitive Function.

Means ± standard deviations for raw neurocognitive data. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group).

BASELINE COGNITIVE ELECTROPHYSIOLOGY

Measure	*Ctx+*	*Ctx-*	*HC*
CAPTURE TASK			
Behavior	N=9	N=14	N=15
Neutral RT	.79±.11	.87±.15	.89±.20
Singleton RT	.77±.10	.87±.16	.87±.20
Contingent RT	.81±.11	.91±.16	.94±.20
Singleton d'	-.14±.09	-.01±.12	-.10±.15
Contingent d'	.08±.13	.22±.19	.22±.16
Cont-Sing d'	.24±.15	.24±.22	.33±.17
Electrophysiology	N=8	N=14	N=15
Singleton N2pc	-.50±.40	-.41±.88	.08±.28
Contingent N2pc	-1.0±.65	-.88±1.01	-.45±.49
Difference N2pc	-.50±.56	-.47±.35	-.52±.42
FILTER TASK			
Behavior	N=9	N=13	N=14
Load-1 Accuracy	.86±.08	.92±.07	.89±.12
Load-3 Accuracy	.62±.08	.67±.09	.70±.13
Filter-1 Accuracy	.86±.08	.91±.06	.88±.12
Filter-3 Accuracy	.61±.09	.63±.09	.67±.11
Load Effect	.16±.06	.15±.05	.12±.07
Filter Effect	.001±.02	.003±.02	.006±.02
Electrophysiology	N=8	N=12	N=14
Load-1 CDA	.07±.28	-.13±.47	-.21±.47
Load-3 CDA	-.69±.68	-.86±.77	-.92±.60
Filter-1 CDA	-.27±.37	-.35±.36	-.27±.27
Filter-3 CDA	-.56±.30	-.93±.73	-.83±.66
Load Effect	-.76±.80	-.73±.77	-.71±.78
Filter Effect	-.35±.21	-.21±.64	-.06±.47

Table 4. Baseline Cognitive Electrophysiology.

Means ± standard deviations for raw cognitive electrophysiology data. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group).

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	Ctx+ Group			Ctx- Group			HC Group		
Measure	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*
SF-36									
GenH	71.1±7.7	68.3±8.2	52.7±7.9	61.7±7.9	63.8±8.0	68.5±8.0	88.3±7.1	88.7±7.2	88.4±7.2
Phys-F	33.7±10.9	31.8±13.5	26.0±12.1	68.5±11.1	64.9±11.6	63.5±11.5	81.9±9.5	91.4±10.1	94.4±10.4
Emot-F	63.6±5.7	62.9±7.2	62.3±6.3	75.3±5.8	82.1±6.0	80.7±6.0	87.3±4.9	84.3±5.2	85.4±5.4
Soc-F	59.0±7.1	75.8±8.0	66.7±7.5	68.0±7.2	71.0±7.4	76.2±7.3	77.3±6.3	79.5±6.5	77.7±6.6
Phys-R	65.1±10.9	71.8±13.5	63.1±12.1	89.5±11.1	86.8±11.6	86.8±11.5	87.5±9.5	85.7±10.0	78.7±10.4
Emot-R	42.8±7.0	46.7±7.8	35.2±7.3	49.7±7.1	54.2±7.3	57.6±7.2	64.8±6.3	69.7±6.4	66.3±6.5
Fatigue	79.2±3.4	87.2±3.9	83.8±3.6	83.8±3.4	84.4±3.5	88.3±3.5	82.0±3.0	82.4±3.1	84.3±3.2
Pain	51.5±6.3	52.8±6.9	41.4±6.6	53.8±6.4	54.0±6.6	52.7±6.5	73.8±5.7	73.8±5.9	74.9±5.9

Table 5. Quality of Life LSM.

Means and standard errors for least squared mean model parameters from full mixture model. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group; T1=baseline; T2=one-month followup; T3=three-month followup).

	Ctx+ Group			Ctx- Group			HC Group		
Measure	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*
TMT									
TMT-A	32.0±2.5	26.9±2.8	27.5±2.9	27.3±2.5	22.8±2.6	27.2±2.7	28.2±2.3	23.6±2.4	22.8±2.5
TMT-B	96.1±11.8	71.2±12.7	67.2±13.0	67.0±11.6	69.7±12.1	55.8±12.3	68.0±11.1	71.2±11.4	61.0±11.7
STROOP									
Stroop-W	92.6±3.9	100.4±4.2	100.7±4.3	91.5±3.8	95.9±4.0	97.0±4.1	95.6±3.6	101.0±3.7	99.2±3.8
Stroop-C	64.8±3.2	68.0±3.5	67.6±3.6	71.2±3.2	70.6±3.4	75.8±3.5	72.4±3.0	73.8±3.1	74.0±3.1
StroopCW	27.3±3.0	31.0±3.4	36.7±3.5	34.3±3.0	39.7±3.3	40.8±3.4	37.5±2.8	43.6±3.0	45.9±3.0
Stroop-I	10.5±2.6	9.0±3.0	3.2±3.2	5.4±2.6	1.0±2.9	1.9±3.1	3.6±2.4	-1.1±2.6	-3.6±2.7
PASAT									
Attempted	20.3±2.3	20.7±2.4	24.2±2.4	24.0±2.1	25.4±2.1	23.7±2.1	26.7±1.9	28.0±1.9	28.6±1.9
UFOV									
Subtest 3	194.0±26.0	108.4±27.3	98.4±29.1	119.6±21.8	108.4±27.3	121.1±24.4	127.9±20.1	94.5±21.5	92.2±22.3

Table 6. Neurocognitive LSM.

Means and standard errors for least squared mean model parameters from full mixture model. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group; T1=baseline; T2=one-month followup; T3=three-month followup).

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	Ctx+ Group			Ctx- Group			HC Group		
Measure	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*	*T1*	*T2*	*T3*
CAPTURE TASK									
Behavior									
Neutral RT	.81±.04	.76±.04	.74±.04	.84±.03	.79±.03	.77±.03	.89±.03	.79±.03	.89±.03
Singleton RT	.78±.04	.75±.04	.73±.04	.84±.03	.80±.03	.78±.03	.87±.03	.79±.03	.79±.03
Contingent RT	.82±.04	.78±.04	.76±.04	.88±.03	.82±.03	.80±.03	.94±.03	.84±.03	.81±.03
Singleton d'	-.14±.05	-.04±.05	-.07±.05	-.01±.04	.01±.04	.06±.05	-.10±.04	.03±.04	-.003±.04
Contingent d'	.08±.06	.19±.06	.14±.06	.23±.05	.19±.06	.25±.06	.22±.05	.28±.05	.17±.05
Cont-Sing d'	.24±.07	.24±.07	.21±.07	.25±.06	.18±.06	.18±.06	.33±.05	.26±.06	.17±.06
Electrophysiology									
Singleton N2pc	-.45±.24	-.27±.24	-.23±.25	-.44±.19	-.46±.22	-.60±.22	.07±.18	-.43±.21	-.58±.21
Contingent N2pc	-.96±.28	.53±.28	-.59±.28	-.94±.22	-1.0±.25	-.64±.25	-.48±.21	-.84±.24	-1.14±.24
Difference N2pc	-.50±.26	-.27±.26	-.37±.26	-.50±.20	-.55±.23	-.04±.23	-.54±.19	-.40±.22	-.56±.22
FILTER TASK									
Behavior									
Load-1 Accuracy	.86±.03	.92±.03	.95±.03	.91±.03	.91±.03	.91±.03	.89±.03	.89±.03	.90±.03
Load-3 Accuracy	.62±.04	.72±.04	.72±.02	.67±.03	.67±.03	.69±.03	.70±.03	.69±.03	.71±.03
Filter-1 Accuracy	.86±.03	.93±.03	.94±.03	.91±.03	.88±.03	.92±.03	.88±.03	.89±.03	.90±.03
Filter-3 Accuracy	.61±.03	.66±.03	.69±.03	.63±.03	.66±.03	.64±.03	.67±.03	.67±.03	.70±.03
Load Effect	.16±.02	.12±.02	.14±.02	.15±.02	.16±.02	.15±.02	.12±.02	.13±.02	.11±.02
Filter Effect	.001±.01	-.01±.01	.01±.01	.004±.01	.02±.01	-.004±.01	.01±.01	.004±.01	-.002±.01
Electrophysiology									
Load-1 CDA	.05±.17	-.30±.17	-.19±.17	-.16±.14	.03±.16	-.48±.16	-.21±.13	-.22±.15	-.08±.15
Load-3 CDA	-.64±.26	-1.01±.26	-1.01±.26	-.93±.21	-.86±.23	-.83±.25	-.92±.20	-.75±.22	-.96±.23
Filter-1 CDA	-.25±.17	-.31±.17	-.75±.17	-.35±.14	-.40±.15	-.72±.16	-.26±.13	-.34±.15	-.34±.15
Filter-3 CDA	-.52±.30	-1.14±.29	-.81±.30	-.96±.25	-.73±.27	-1.13±.28	-.81±.23	-.72±.25	-.63±.26
Load Effect	-.76±.25	-.65±.25	-.81±.25	-.77±.20	-.92±.22	-.37±.24	-.71±.19	-.53±.21	-.90±.22
Filter Effect	-.33±.17	.00±.16	-.55±.17	-.21±.14	-.44±.15	-.23±.16	-.05±.13	-.10±.14	-.25±.15

Table 7. Cognitive Electrophysiology LSM.

Means and standard errors for least squared mean model parameters from full mixture model. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group; T1=baseline; T2=one-month followup; T3=three-month followup).

	GH	PF	EF	SF	PR	ER	F	P
Tr-A	0.06740 0.7657	-0.25186 0.2582	-0.23130 0.3003	-0.08493 0.7071	-0.14047 0.5329	-0.13960 0.5355	-0.18550 0.4085	-0.13556 0.5475
Tr-B	0.00196 0.9931	**-0.48259** **0.0229**	**-0.36583** **0.0941**	-0.25927 0.2439	**-0.35939** **0.1004**	-0.22073 0.3236	**-0.36427** **0.0956**	-0.20608 0.3575
Str-W	0.03845 0.8651	0.24291 0.2760	0.24086 0.2802	**0.39278** **0.0706**	0.15663 0.4864	0.00560 0.9803	0.17627 0.4326	0.15208 0.4993
Str-C	0.25512 0.2518	**0.47832** **0.0243**	0.13505 0.5490	**0.39065** **0.0722**	0.06313 0.7802	0.27093 0.2226	0.11948 0.5964	0.19769 0.3778
Str-CW	0.16718 0.4571	**0.35641** **0.1035**	0.24230 0.2773	**0.51054** **0.0152**	**0.40879** **0.0589**	**0.35560** **0.1043**	**0.36071** **0.0991**	0.28179 0.2039
Str-I	-0.10431 0.6441	-0.20702 0.3553	-0.18199 0.4176	**-0.39351** **0.0700**	**-0.43292** **0.0442**	**-0.32690** **0.1376**	**-0.34537** **0.1154**	-0.22055 0.3240
PAS	-0.03405 0.8804	**0.33775** **0.1242**	**0.45717** **0.0324**	**0.38603** **0.0760**	**0.39130** **0.0717**	0.23426 0.2940	0.26267 0.2376	0.25542 0.2513
PAS	-0.07795 0.7302	0.27954 0.2077	**0.42089** **0.0511**	**0.43972** **0.0406**	**0.29569** **0.1815**	0.16124 0.4735	0.17675 0.4314	0.27959 0.2076
UFOV	0.12613 0.5759	0.01678 0.9409	0.01857 0.9346	-0.16072 0.4749	-0.05574 0.8054	0.12185 0.5891	0.06687 0.7675	0.17934 0.4245

Table 8. Matrix of correlations between quality of life and neurocognitive measures.

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	GH	PF	EF	SF	PR	ER	F	P
nRT	-0.15914 0.4683	-0.10332 0.6390	-0.07093 0.7478	-0.18816 0.3899	**-0.30470** **0.1575**	**-0.27903** **0.1973**	**-0.29054** **0.1787**	-0.08509 0.6995
sRT	-0.20083 0.3582	-0.13339 0.5440	-0.10459 0.6348	-0.20121 0.3573	**-0.37351** **0.0792**	**-0.31308** **0.1458**	**-0.32949** **0.1247**	-0.13381 0.5427
cRT	-0.11856 0.5900	-0.00397 0.9856	0.00492 0.9822	-0.14648 0.5048	-0.26160 0.2279	-0.13911 0.5267	-0.24661 0.2566	-0.00734 0.9735
d'-S	-0.14730 0.5024	-0.19394 0.3752	**-0.28836** **0.1821**	-0.18639 0.3945	**-0.41047** **0.0517**	-0.21393 0.3270	-0.23091 0.2891	-0.24402 0.2618
d'-C	0.17819 0.4160	**0.41922** **0.0465**	**0.33585** **0.1172**	0.26055 0.2299	0.18345 0.4021	**0.53359** **0.0087**	0.16647 0.4478	**0.30889** **0.1515**
d'	0.23614 0.2780	**0.49314** **0.0168**	**0.50192** **0.0147**	**0.31622** **0.1416**	**0.45800** **0.0280**	**0.62005** **0.0016**	**0.29370** **0.1738**	**0.45166** **0.0305**
L1	0.02875 0.8964	0.04500 0.8385	0.10931 0.6196	-0.02664 0.9039	0.00598 0.9784	-0.14282 0.5156	-0.14272 0.5159	-0.18024 0.4105
L3	0.12339 0.5749	0.18488 0.3984	0.32173 0.1344	**0.28877** **0.1814**	0.09747 0.6582	-0.06236 0.7774	-0.24293 0.2640	0.02871 0.8965
F1	0.06643 0.7633	0.05229 0.8127	0.10034 0.6487	0.00893 0.9677	0.02311 0.9166	-0.17457 0.4256	-0.08602 0.6963	-0.13462 0.5403
F3	0.27632 0.2018	0.23518 0.2800	**0.32237** **0.1336**	**0.33704** **0.1158**	0.07307 0.7404	-0.10005 0.6497	-0.12760 0.5618	-0.01209 0.9563
Load	-0.15930 0.4678	-0.24416 0.2615	**-0.32155** **0.1346**	**-0.43598** **0.0376**	-0.16311 0.4571	-0.11185 0.6114	0.15393 0.4831	-0.23171 0.2874
Filt	-0.13489 0.5395	-0.01419 0.9488	0.03981 0.8569	-0.10880 0.6212	-0.03512 0.8736	0.10768 0.6248	-0.16511 0.4515	-0.16225 0.4595

Table 9. Matrix of correlations between quality of life and behavioral measures of cognitive electrophysiology.

	GH	PF	EF	SF	PR	ER	F	P
N2s	0.06625 0.7696	0.01871 0.9341	0.04322 0.8485	-0.08298 0.7135	-0.02971 0.8956	-0.02343 0.9176	-0.02538 0.9107	0.15975 0.4776
N2c	-0.02236 0.9213	-0.05891 0.7945	0.13012 0.5638	-0.01331 0.9531	-0.00951 0.9665	-0.18907 0.3994	-0.10646 0.6373	-0.03100 0.8911
L1	-0.05841 0.7963	-0.19527 0.3838	-0.18579 0.4078	**-0.35064** **0.1096**	-0.11623 0.6065	-0.22784 0.3078	-0.09981 0.6585	-0.16865 0.4531
L3	**-0.36388** **0.0960**	-0.18159 0.4186	-0.12687 0.5737	-0.13216 0.5577	-0.16627 0.4596	0.04377 0.8466	-0.00064 0.9977	0.15785 0.4829
F1	-0.00181 0.9936	0.11091 0.6232	-0.16652 0.4589	0.01975 0.9305	-0.13563 0.5473	0.05922 0.7935	-0.05981 0.7915	-0.26152 0.2397
F3	**-0.30653** **0.1653**	**-0.30035** **0.1744**	**-0.32307** **0.1425**	**-0.34609** **0.1146**	-0.25446 0.2531	-0.26388 0.2354	-0.10803 0.6323	-0.07823 0.7293
N2	-0.17011 0.4491	-0.15638 0.4871	0.18712 0.4044	0.12796 0.5704	0.03603 0.8735	**-0.34560** **0.1152**	-0.17178 0.4446	**-0.36297** **0.0969**
Load	-0.27980 0.2073	-0.04573 0.8399	-0.00404 0.9858	0.08460 0.7082	-0.07724 0.7326	0.16642 0.4592	0.05587 0.8050	0.23103 0.3009
Filt	0.05403 0.8113	0.25940 0.2437	0.06363 0.7785	**0.34499** **0.1159**	0.01863 0.9344	0.25540 0.2513	0.05414 0.8109	-0.01655 0.9417

Table 10. Matrix of correlations between quality of life and neural measures of cognitive electrophysiology.

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	Tr-A	Tr-B	Str-W	Str-C	Str-CW	Str-I	PAS	PAS	UFOV
nRT	**0.35938**	0.13689	**-0.28257**	**-0.39610**	-0.20843	0.05387	0.03168	0.07781	-0.12893
	0.0777	0.5141	**0.1711**	**0.0500**	0.3174	0.7982	0.8805	0.7116	0.5391
sRT	**0.28794**	0.12413	-0.26171	**-0.34344**	-0.21260	0.07974	0.02450	0.09105	-0.14821
	0.1628	0.5544	0.2063	**0.0928**	0.3076	0.7048	0.9075	0.6651	0.4795
cRT	**0.35320**	0.06387	-0.23938	-0.25619	-0.14426	0.03618	0.07990	0.12067	-0.14198
	0.0833	0.7617	0.2491	0.2164	0.4915	0.8637	0.7042	0.5656	0.4984
d'-S	-0.22549	-0.03647	0.14691	**0.28136**	-0.13086	0.27026	-0.08725	-0.01242	-0.08434
	0.2785	0.8626	0.4835	**0.1731**	0.5330	0.1913	0.6783	0.9530	0.6886
d'-C	-0.14833	**-0.33908**	0.12435	**0.52664**	0.27251	-0.11245	0.15686	0.16022	-0.13594
	0.4792	**0.0973**	0.5537	**0.0068**	0.1875	0.5925	0.4540	0.4443	0.5170
d'	0.00109	**-0.28732**	-0.00831	**0.29480**	**0.33138**	-0.28615	0.19501	0.14393	-0.05480
	0.9959	**0.1637**	0.9686	**0.1526**	**0.1056**	0.1655	0.3502	0.4925	0.7947
L1	**-0.53552**	**-0.42165**	-0.15849	0.17989	-0.05941	0.07634	0.23208	0.24112	**-0.30678**
	0.0058	**0.0358**	0.4492	0.3895	0.7779	0.7168	0.2643	0.2456	**0.1358**
L3	-0.17392	**-0.40251**	**0.44316**	**0.49614**	0.08829	0.15263	0.27680	**0.30557**	-0.17677
	0.4057	**0.0461**	**0.0265**	**0.0117**	0.6747	0.4664	0.1804	**0.1374**	0.3979
F1	**-0.50332**	**-0.36771**	0.00791	0.23163	-0.00074	0.06930	0.23396	0.27853	-0.21375
	0.0103	**0.0705**	0.9701	0.2652	0.9972	0.7420	0.2603	0.1776	0.3049
F3	-0.07820	-0.16181	**0.60056**	**0.39010**	0.11485	0.13228	**0.33509**	**0.40106**	-0.03581
	0.7102	0.4397	**0.0015**	**0.0539**	0.5846	0.5285	**0.1015**	**0.0469**	0.8651
Load	**-0.33370**	0.12146	**-0.69668**	**-0.45857**	-0.17193	-0.11284	-0.08968	-0.10792	-0.07834
	0.1031	0.5630	**0.0001**	**0.0211**	0.4112	0.5912	0.6699	0.6076	0.7097
Filt	-0.11822	-0.20351	**-0.52643**	-0.16850	-0.16684	0.00061	0.02311	-0.09543	**-0.31048**
	0.5736	0.3292	**0.0069**	0.4207	0.4254	0.9977	0.9127	0.6500	**0.1309**

Table 11. Matrix of correlations between neurocognitive and behavioral measures of cognitive electrophysiology.

	Tr-A	Tr-B	Str-W	Str-C	Str-CW	Str-I	PAS	PAS	UFOV
N2s	**0.37003**	0.09036	0.03021	-0.12132	0.08766	-0.12545	0.12397	0.09241	0.01590
	0.0822	0.6818	0.8912	0.5813	0.6908	0.5684	0.5731	0.6750	0.9426
N2c	0.24329	-0.00586	-0.02234	-0.23978	-0.07641	0.00315	0.20525	0.16956	-0.09537
	0.2633	0.9788	0.9194	0.2705	0.7289	0.9886	0.3475	0.4393	0.6651
L1	0.00202	-0.15330	-0.02444	-0.08307	-0.08318	0.05639	-0.28519	-0.31968	-0.05182
	0.9927	0.4849	0.9119	0.7063	0.7059	0.7983	0.1871	0.1370	0.8144
L3	-0.01563	0.06896	**-0.35134**	-0.18967	-0.04948	-0.08600	0.06561	0.11076	0.01452
	0.9436	0.7545	**0.1002**	0.3861	0.8226	0.6964	0.7661	0.6149	0.9476
F1	0.01351	0.06302	-0.09290	0.18225	**0.32827**	**-0.34630**	-0.04953	-0.06861	0.07600
	0.9512	0.7751	0.6733	0.4052	**0.1262**	**0.1055**	0.8224	0.7557	0.7304
F3	0.26680	0.19298	0.01553	0.01246	0.08689	-0.09362	-0.21398	-0.16684	0.22156
	0.2185	0.3776	0.9439	0.9550	0.6934	0.6709	0.3269	0.4467	0.3096
N2	-0.23990	-0.20553	-0.11460	-0.28159	**-0.35864**	0.27414	0.19823	0.18504	-0.24857
	0.2702	0.3468	0.6026	0.1930	**0.0929**	0.2056	0.3646	0.3980	0.2528
Load	-0.01328	0.13742	-0.26040	-0.10243	0.00686	-0.09778	0.20680	0.26080	0.03960
	0.9521	0.5318	0.2301	0.6419	0.9752	0.6571	0.3438	0.2294	0.8576
Filt	0.00793	0.17070	-0.04584	0.19759	**0.30130**	**-0.29208**	0.19921	0.21401	0.09651
	0.9714	0.4361	0.8355	0.3661	**0.1624**	**0.1763**	0.3621	0.3268	0.6613

Table 12. Matrix of correlations between neurocognitive and neural measures of cognitive electrophysiology.

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	L1	L3	F1	F3	Load	Filt	L1	L3	F1	F3	Load	Filt
nRT	0.0435 0.8366	0.0005 0.9982	0.0260 0.9017	0.0369 0.8611	0.0209 0.9209	0.0519 0.8054	-0.212 0.3091	-0.0404 0.8481	0.0490 0.8160	0.0540 0.7975	0.0827 0.6942	0.2117 0.3097
sRT	0.1409 0.5016	0.0844 0.6884	0.1339 0.5233	0.0844 0.6884	0.0115 0.9567	0.0181 0.9317	-0.2366 0.2549	-0.0978 0.6419	0.0461 0.8267	0.0406 0.8472	0.0465 0.8254	0.2307 0.2673
cRT	0.0481 0.8195	0.0465 0.8253	0.0286 0.8920	0.0256 0.9035	-0.0361 0.8642	0.0530 0.8015	-0.2483 0.2313	-0.0084 0.9681	0.0337 0.8729	0.1020 0.6274	0.1308 0.5333	0.2324 0.2635
d'-S	**0.4383** **0.0284**	**0.4113** **0.0411**	**0.4929** **0.0123**	0.2351 0.2580	-0.0869 0.6797	-0.1803 0.3885	-0.0641 0.7609	**-0.2770** **0.1800**	-0.1112 0.5968	-0.0126 0.9524	-0.205 0.3249	-0.0189 0.9284
d'-C	0.1888 0.3661	**0.2978** **0.1482**	0.1633 0.4355	0.0367 0.8618	-0.2097 0.3143	0.0643 0.7599	-0.1723 0.4102	0.0068 0.9741	-0.096 0.6482	-0.0189 0.9286	0.1017 0.6285	0.0827 0.6944
d'	-0.1320 0.5293	-0.0708 0.7366	-0.1985 0.3414	-0.2044 0.3271	-0.0607 0.7731	0.1987 0.3410	-0.004 0.9850	0.2582 0.2128	0.0037 0.9859	0.1089 0.6042	0.2267 0.2758	0.00582 0.9780
N2s	**-0.272** **0.1885**	-0.1643 0.4327	-0.2563 0.2163	-0.0517 0.8062	-0.0587 0.7799	-0.0585 0.7812	0.03909 0.8528	0.00441 0.9833	0.24002 0.2478	**0.44109** **0.0273**	-0.018 0.9323	0.12494 0.5518
N2c	-0.0219 0.9171	0.02154 0.9186	-0.0388 0.8540	0.12980 0.5363	-0.0483 0.8186	0.06187 0.7689	-0.0486 0.8176	-0.1631 0.4360	0.24704 0.2338	0.23277 0.2628	-0.115 0.5847	0.20380 0.3285
N2-cs	**0.49330** **0.0122**	**0.37387** **0.0656**	**0.42534** **0.0340**	**0.38605** **0.0566**	0.01170 0.9557	0.25139 0.2254	-0.1838 0.3791	**-0.3647** **0.0731**	0.06140 0.7706	**-0.3699** **0.0688**	-0.215 0.3022	0.19605 0.3476

Table 13. Matrix of correlations between behavioral and neural measures cognitive electrophysiology.

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FIGURES

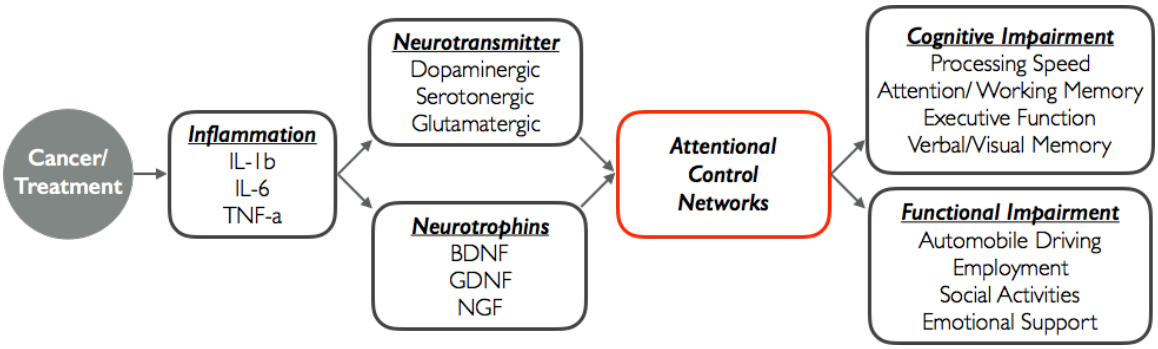

Figure 1. Biological Mechanism for Cognitive Impairment

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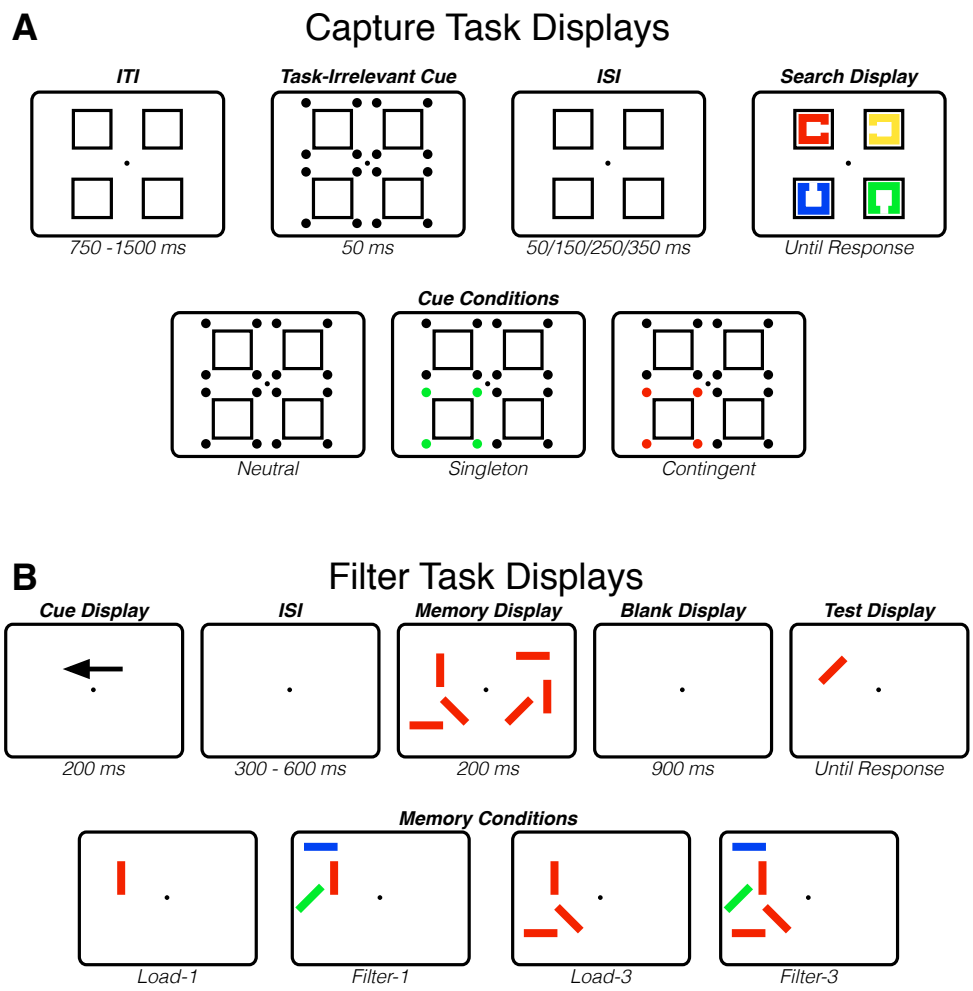

Figure 2. Computer-Based Cognitive Tasks.

(A) Trial structure sequence and cue conditions for the capture task. Participants searched for and responded to the direction of the red "C" that could be presented in any one of placeholders in the search display. Prior to search display presentation, a task-irrelevant cue was presented around a single square placeholder. For 50% of trials, no placeholder was cued (neutral condition); the remaining 50% of trials were divided equally between a single cue that was either the same color as the target (contingent condition) or different color than the target (singleton condition). **(B)** Trials structure and memory conditions for the filter task. Participants were cued to remember the orientation of red memory items presented on either the left or right side of the screen, depending on cue direction. After a short delay, participants were instructed to indicate whether a single test item was the same or different orientation as the item in the same probed location during the memory display. Participants remembered either 1 (Load-1 condition) or 3 (Load-3 condition) memory items. Participants were instructed to ignore any non-red items, which were present during half of the trials among either 1 (Filter-1) or 3 (Filter-3) memory items.

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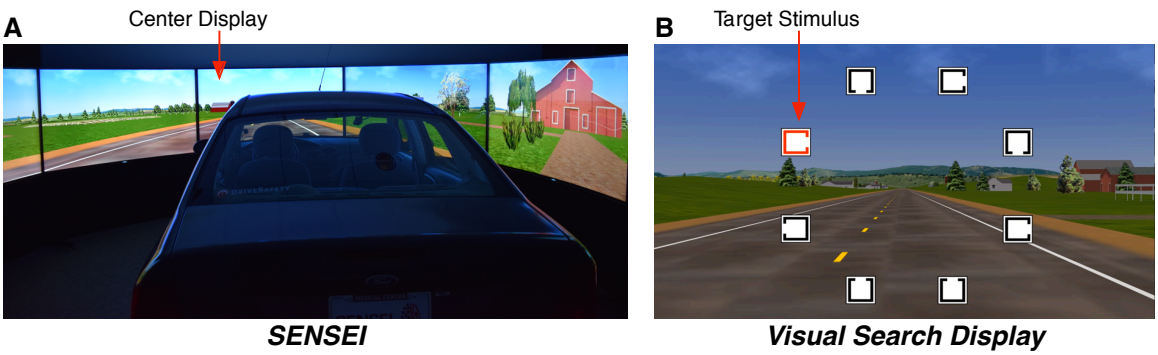

Figure 3. Simulator Task.

(A) Participants completed simulated driving scenarios in SENSEI (Simulator for Ergonomic, Neuroscience, Safety, Engineering, and Innovation). (B) Participants completed visual search tasks by responding with the direction of a red target stimulus presented among black distractors. Visual search displays were presented on the center display in SENSEI. During the driving (shown in B) condition, visual search stimuli were presented against the simulated background. During the baseline condition, stimuli were presented against a black background.

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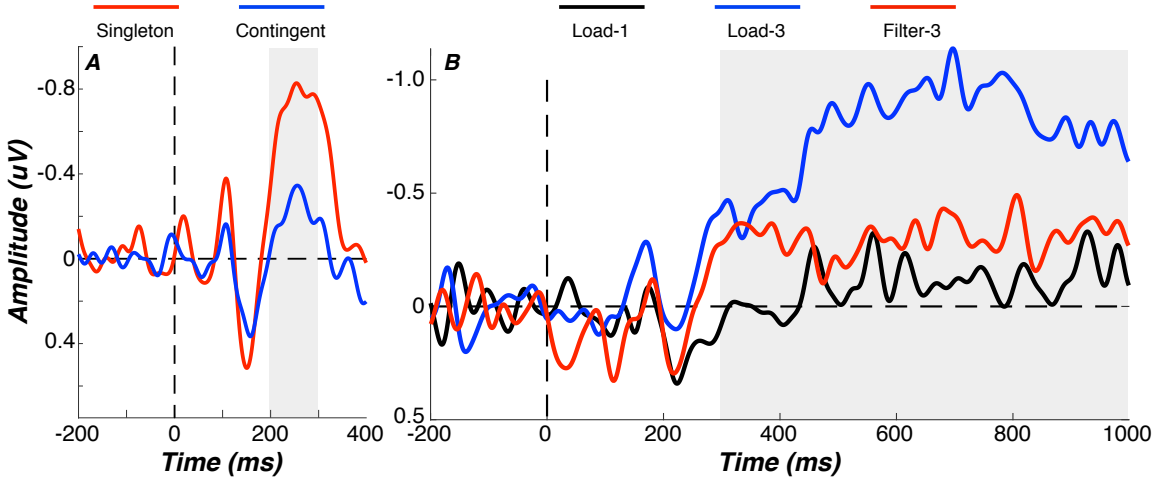

Figure 4. Electrophysiological Waveforms.

Grand averaged waveforms are presented for cognitive electrophysiology measures. EEG amplitudes (in microvolts) are plotted as a function of time (in milliseconds), where time=0 corresponds to stimulus onset. (A) In the capture task, a large negative deflection in EEG amplitude emerges approximately 200 milliseconds following cue onset. This large negative deflection corresponds to the N2pc component, which was present for the both singleton (blue) and contingent (red) conditions. Average N2pc amplitudes were estimated within the gray window. (B) In the filter task, sustained negative potentials were observed in EEG activity across the entire delay period, which emerged approximately 300 milliseconds following presentation of the memory display. This sustained negativity corresponds to the CDA component, which was present for the load-1 (black), load-3 (blue), and filter-1 (red) conditions.

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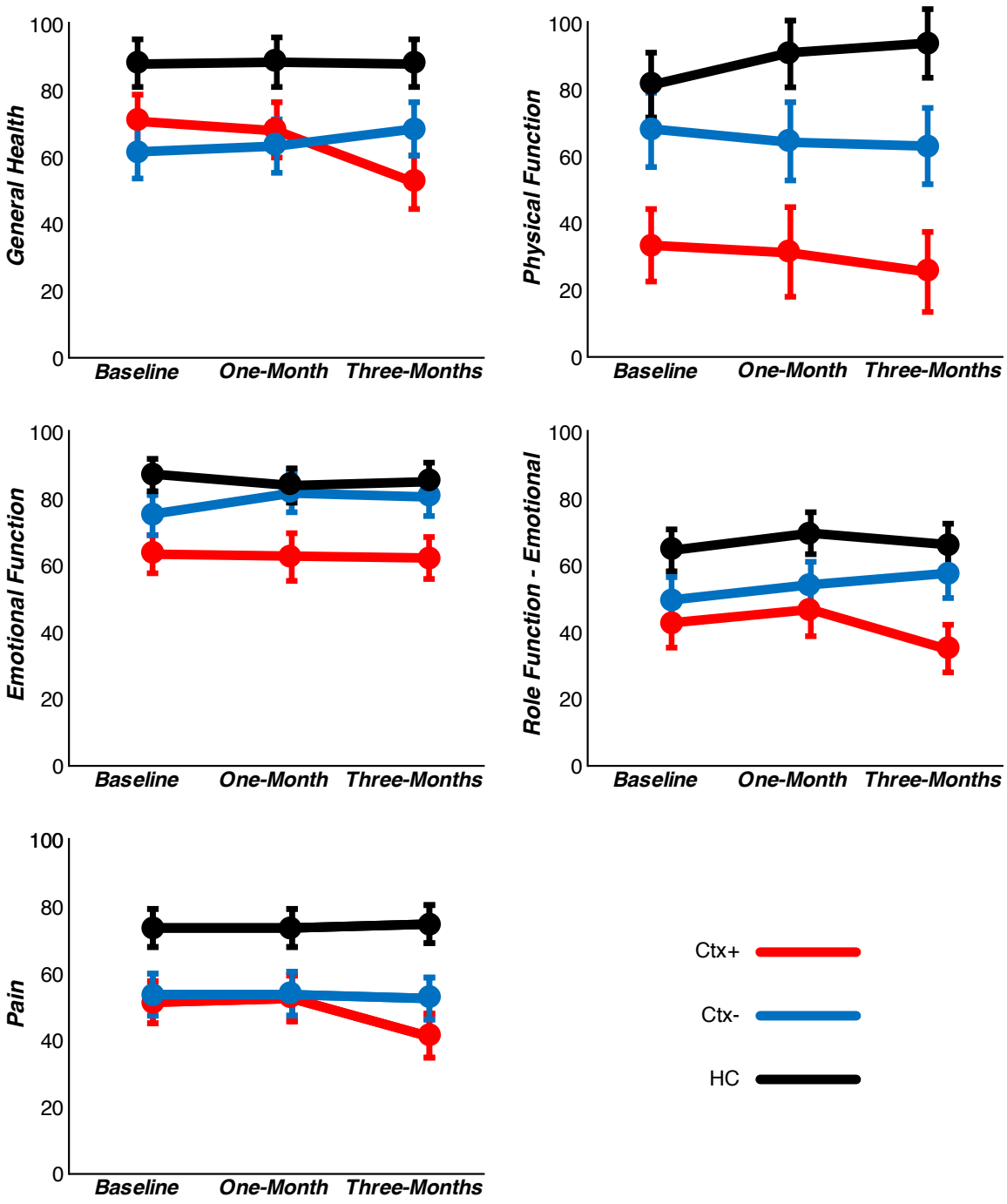

Figure 5. Quality of Life LSM.

Plotted means for least squared mean model parameters from full mixture model. Only outcome measures showing group or group-by-time interactions at p<.20 are displayed. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group; T1=baseline; T2=one-month followup; T3=three-month followup).

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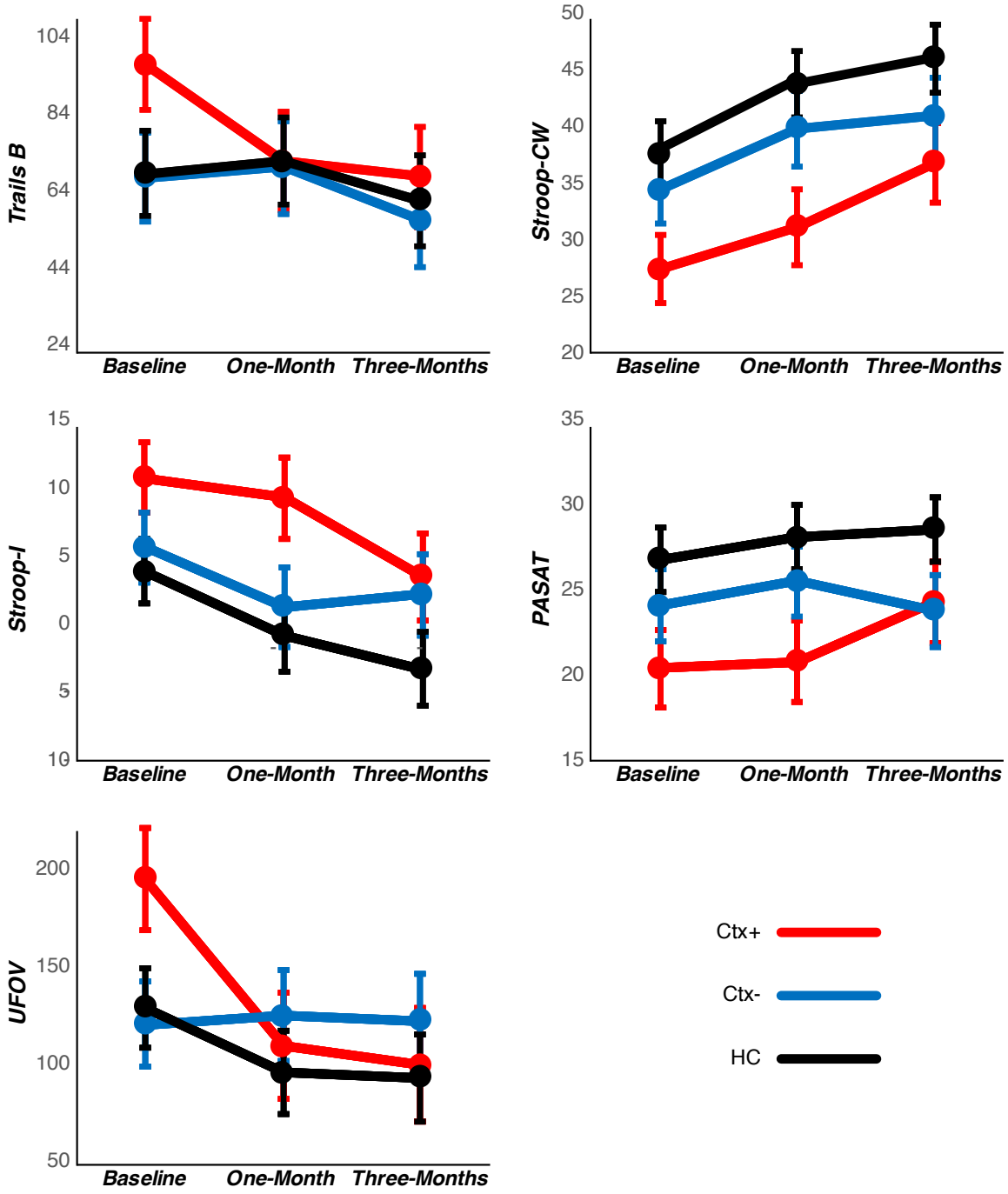

Figure 6. Neurocognitive LSM.

Plotted means for least squared mean model parameters from full mixture model. Only outcome measures showing group or group-by-time interactions at p<.20 are displayed. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group; T1=baseline; T2=one-month followup; T3=three-month followup).

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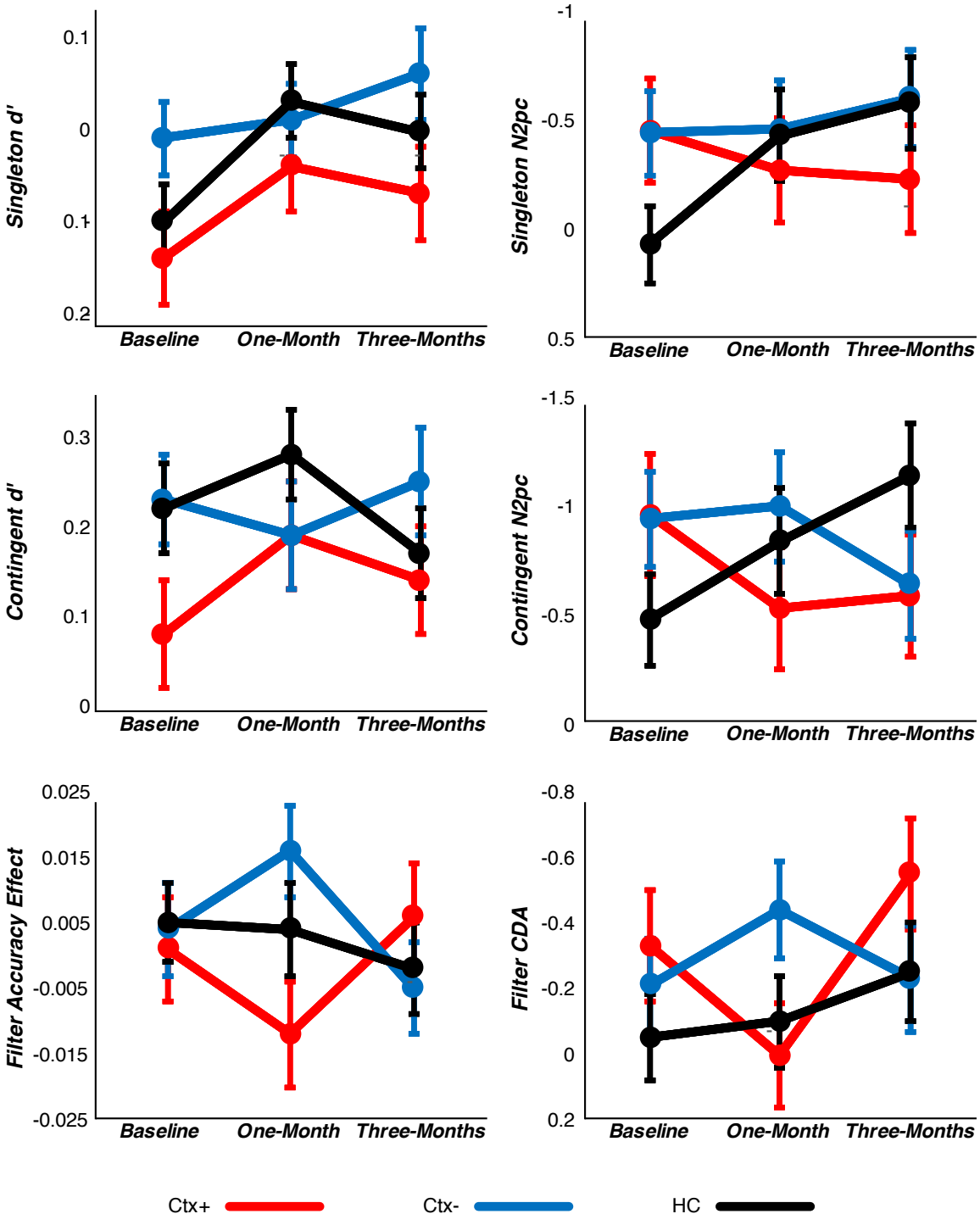

Figure 7. Cognitive Electrophysiology LSM.

Plotted means for least squared mean model parameters from full mixture model. Only outcome measures showing group or group-by-time interactions at p<.20 are displayed. (Ctx+ = Chemotherapy patient group; Ctx- = non-chemotherapy patient group; HC = healthy control group; T1=baseline; T2=one-month followup; T3=three-month followup).

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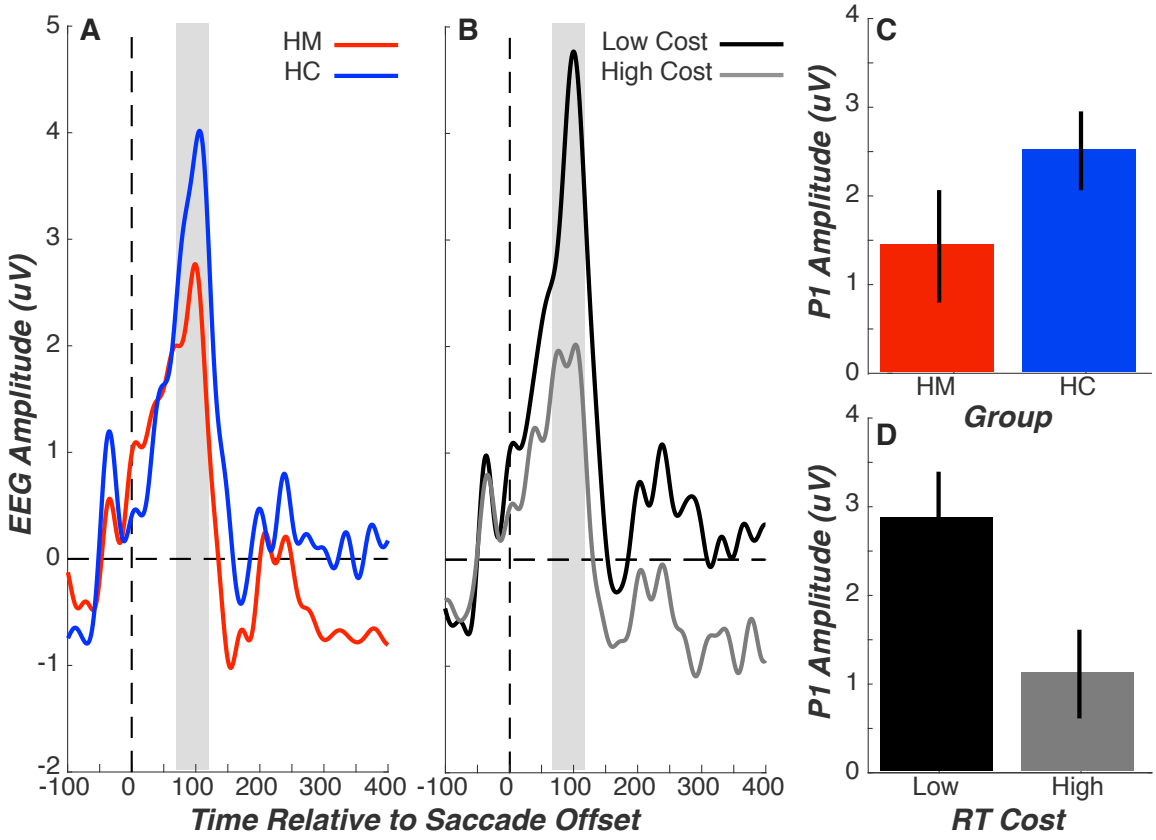

Figure 8. EFRP Results.

(A,B) EFRP activity was measured by estimating mean EEG amplitude as a function of time relative to saccade offset (time=0). P1 activity (gray boxes) emerged approximately 100 milliseconds after saccade offset. (A) EFRP activity is plotted separately for healthy control (HC; blue line) drivers and drivers diagnosed with a hematological malignancy (HM; red line). (B) Drivers were split into two groups based on differences in visual search response time (RT) between driving and baseline conditions. EFRP activity is plotted separately for drivers showing smaller (low cost; black line) and larger (high cost; gray line) RT differences. (C, D) P1 amplitude was estimated as mean EFRP activity during the P1 time window (gray boxes in A, B). (C) P1 amplitudes were larger for HC (blue) drivers compared to HM drivers (red; p=.18). (D) P1 amplitudes were larger for drivers with low RT costs (black) compared to drivers with high RT costs (gray; p=.03).

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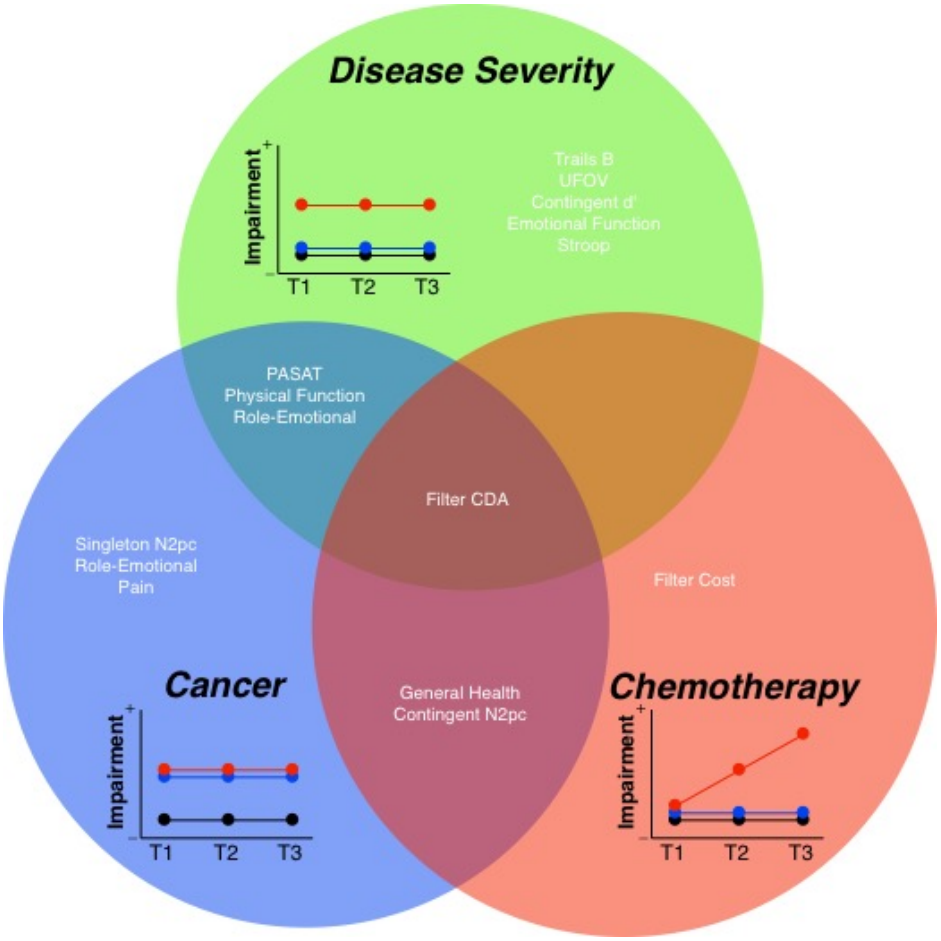

Figure 9. Venn diagram of empirical patterns observed in neurocognitive data.

Three empirical patterns are highlighted: (1) Chemotherapy (red); (2) Cancer (blue); (3) Disease Severity (green). Archetypes for each empirical pattern were provided as plot insets, with individual predictions for Ctx+ (red line), Ctx- (blue line), and HC (black line) groups. Outcome measures are presented within individual or between sets to indicate the empirical pattern(s) observed for that set.

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