FRED & PAMELA BUFFETT CANCER CENTER SRC PROTOCOL

PROTOCOL TITLE

Electrophysiological biomarkers of chemotherapy-related cognitive impairment

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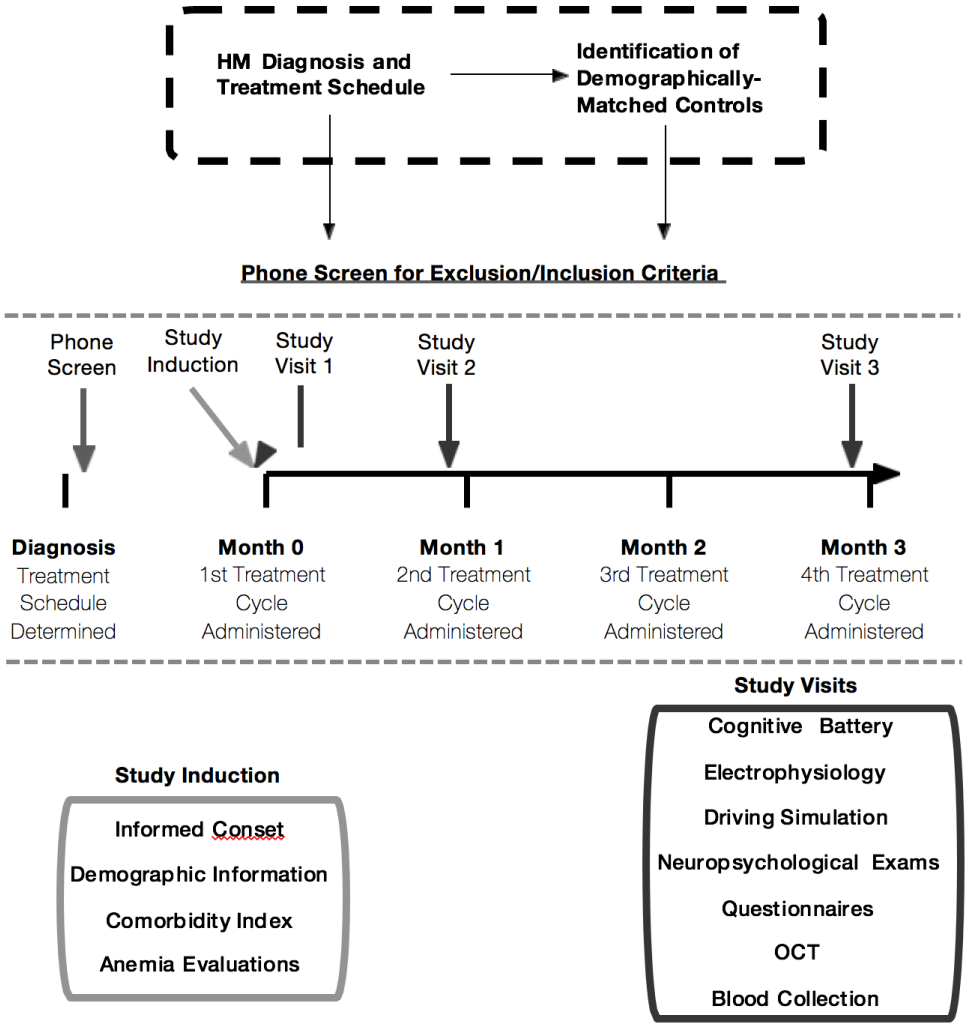
Abstract:

The goal of this study is to better understand the influence of chemotherapy treatment on the neural mechanisms of attention and cognition. Extant literature lacks diversity in studied cancer populations and treatment protocols, and provides limited understanding of the cognitive abilities that are impaired by chemotherapy. To overcome these limitations, this study will employ a sophisticated battery of tests in understudied cancer populations with hematological malignancies (HM). Eligible participants will either be patients diagnosed with Myelodysplasic Syndrome (MDS), Acute Myelogenous Leukemia (AML), Acute Lymphocytic Leukemia (ALL), Multiple Myeloma (MM), Non-Hodgkin Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), and Chronic Myelogenous Leukemia (CML). Demographically-matched healthy control participants will be included for comparison.

After diagnosis and treatment protocols have been established, patients will be inducted into the longitudinal study comprised of three visits: 1) after diagnosis but prior to chemotherapy treatment (baseline), 2) one-month post-baseline **or after one treatment cycle (whichever comes first)**, and 3) three-months post-baseline **or after three treatment cycles (whichever comes first).** Patients will undergo a test battery designed to measure specific behavioral and neural mechanisms of attention; tests will either be computer-based cognitive tasks or simulated driving tests that immerse patients into virtual driving scenarios. During each test, EEG will be concurrently measured through non-invasive scalp electrophysiology recordings; EEG recordings will reveal underlying neural mechanisms affected by chemotherapy. Additionally, neuropsychological tests of vision, attention, and memory will be administered, as well as questionnaires to evaluate health, mobility, and life space. Finally, blood samples will be collected to examine levels of circulating inflammatory markers present in some cancer patients. This study will allow us to better understand the mechanisms through which chemotherapy influences cognitive performance. Results from this study may allow informed treatment decision-making and therapy selection based on patients' goal of care and value to preserve cognitive and functional capacity.

Schema:



Section 1.0 Objectives:

The broad goal of this research project is to develop a core set of biomarkers for detecting chemotherapy related cognitive impairment (or 'chemobrain'). Multiple clinical studies have documented cognitive impairment in chemotherapy patients, demonstrating impairments most frequently in attention and memory abilities, among other cognitive functions. Neuroimaging studies in these patients have shown structural and functional changes across cortical networks often linked with neural mechanisms of attention, including fronto-parietal cortical regions. Together, behavioral and neuroimaging studies converge on the hypothesis that attention networks are most impacted by chemotherapy.

Explanatory mechanisms for chemotherapy-related cognitive impairment require further research and clarification for several reasons: 1) current research has focused on breast cancer populations and

ignored other prevalent tumor types; 2) few studies have examined dose-response effects of specific chemotherapy treatments on cognitive impairment; 3) neuropsychological tests used to characterize chemotherapy-related cognitive impairment provide limited resolution for understanding impairments of specific neural mechanisms; 4) neural factors associated with cognitive impairment have not been sufficiently distinguished from non-neural (e.g. psychosocial) factors. Despite these limitations of current research, chemotherapy-related cognitive impairment affects everyday function and quality of life in cancer survivors. This is a problem that merits further investigation and cannot be ignored.

To overcome these critical limitations of current research on chemotherapy-related cognitive impairment, we propose a two-year pilot study that aims to systematically examine the influence of cancer stage and treatment toxicity on attention abilities in patients diagnosed with a hematological malignancy (HM). We will establish and measure a core battery of behavioral and electrophysiological measures of attention to assess the impact of chemotherapy on this central cognitive ability.

Our specific aims are to:

SA1. Quantify chemotherapy-related attention impairments in HM patients

H1a. HM groups will not differ from comparison subjects in attention abilities prior to chemotherapy and will perform worse than comparison subjects without cancer or chemotherapy after treatment.

H1b. Degree of chemotherapy exposure will predict magnitude of attention impairments.

SA2. Quantify the link between chemotherapy-related attention impairments and electrophysiological measures of attention in HM patients and comparison subjects

H2a. HM groups will not differ from comparison subjects in electrophysiological measures of attention prior to treatment but will differ from comparison subjects without cancer or chemotherapy after treatment.

H2b. Degree of chemotherapy exposure will predict magnitude of changes in electrophysiological measures of attention.

H2c. Electrophysiological measures of attention decline will be predicted by concurrent impairments in behavioral measures of attention (as in H1b).

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

H3a. HM groups will not differ in driving performance prior to treatment, and will perform worse than comparison subjects without cancer or chemotherapy.

H3b. Degree of chemotherapy exposure will predict magnitude of changes in simulated driving performance.

H3c. Declines in simulated on-road driving performance will be predicted by concurrent impairments in behavioral (as in H1a) and electrophysiological measures (as in H2a) of attention.

Impact

Our approach will allow us to more rigorously study the underlying mechanisms of chemotherapy-related cognitive impairment. The forthcoming pilot project promises to extend knowledge on chemobrain by longitudinally investigating chemotherapy treatments for hematological malignancies, an understudied cancer population. Results from this study will have implications for several collaborative efforts across basic and clinical research silos on campus, with a broad potential for impacting our knowledge, treatment, control, and prevention of chemotherapy-related cognitive impairment. Furthermore, this line of work promises to benefit the Cancer Prevention and Control Program (CPCP) – a research arm of the Fred & Pamela Buffet Cancer Center. Our goal is that this line of research will advance the study and understanding of risk factors associated with chemotherapy, allowing clinicians to make informed treatment

recommendations to mitigate cognitive impairment and preserve cognitive function, independence, and quality of life in our ever-increasing cancer survivor population.

Section 2.0 Introduction:

Multiple behavioral studies have documented chemotherapy-related cognitive impairment across a broad range of cognitive abilities, with deficits most frequently observed in processing speed[1-11], attention[7,9,10,12-20], and memory[1,2,4,5,7,12-15,17,21-24,49]. Although the mechanism through which chemotherapy influences cognitive impairment is poorly understood, chemotherapy-related cognitive decline remains an important public health concern, given the impact of cognitive health on quality of life.

While behavioral measures tell us *what* cognitive abilities are impaired by chemotherapy, they do not tell us *how* cognitive abilities are impaired. Our hypothesis is that chemotherapy negatively affects neural structures underlying attention mechanisms, which in turn would impair information processing and memory abilities. According to current research, attention mechanisms are largely supported by the so-called fronto-parietal attention network[52-56], a largescale cortical network comprised of frontal and parietal cortical regions interconnected by long-range white-matter tracks. Specifically, parietal cortex has been implicated in the deployment of attention mechanisms towards relevant information in the environment[57-60] and frontal cortex has been implicated in modulating goal-directed behaviors that govern mechanisms of attentional control[61-63]. Thus, impairments within fronto-parietal cortical regions would likely translate to concurrent impairments in attention mechanisms.

Neuroimaging studies have revealed changes in both the structure and function of neural tissue after treatment, suggesting chemotherapy may have an impact on the integrity of neural architectures essential to impaired attention mechanisms. While some structural magnetic resonance imaging (MRI) studies have reported global reductions in total gray and white matter volume[5,25-29], more informative studies have demonstrated chemotherapy-related reductions in gray and white matter volumes primarily in frontal[30-33,50,51] and parietal[30,31,34,35] cortical regions. In addition, diffusor tensor imaging (DTI) studies[31,35] have demonstrated reduced white matter track integrity between frontal and parietal cortical regions. Thus, MRI studies have revealed chemotherapy-related impairments in both the structure and connectivity of the fronto-parietal attention network.

Extending findings provided by structural MRI studies, functional MRI studies have documented distributed modulations of neural activity within the fronto-parietal attention network following chemotherapy treatment. During performance in working memory and executive functioning tasks, chemotherapy-related *suppression* of neural activity has been shown in parietal cortex[26,33,36,37,41], whereas chemotherapy-related *enhancement* of neural activity has been shown in frontal cortex[26,36-41]. One possible interpretation of this empirical pattern is that chemotherapy damages parietal networks responsible for the selection of task-relevant information in the environment, leading to a reduction in neural resources available in parietal cortex, and a subsequent hyperactivation of frontal cortex in the enforcement of top-down goals to compensate for impairments in parietal cortex. These functional imaging studies complement structural imaging studies by demonstrating concurrent abnormalities in the fronto-parietal attention network.

Despite the growing body of literature on chemotherapy-related cognitive and neural impairment, research is absent for understanding the impact of chemotherapy on real-world behavior. This lacking body of literature is problematic because computer-based tasks and paper-and-pencil tests provide poor experimental fidelity for understanding the link between cognitive performance and behavior in the wild. Given that motor vehicle driving is a nearly ubiquitous real-world behavior that recruits multiple cognitive domains[101, 102], and that impairments in driving performance and safety have been documented in individuals with low cognitive functioning[103,104] and neurological disease[105-109], chemotherapy-related cognitive impairment may be associated with poor driving performance and safety. Thus, future studies examining the link between chemotherapy-related cognitive impairment and real-world behaviors, such as

driving, will provide novel insight into the impact of chemotherapy treatment on public health and safety.

While MRI offers high spatial resolution of cortical structures, it is limited by its low temporal resolution of an indirect measure of neural activity (i.e. oxygenated blood flow associated with metabolic demands of neurons). In contrast, scalp electroencephalogram (EEG) offers high temporal resolution of population-level neuro-electrical activity occurring at synapses, thus providing millisecond-by-millisecond resolution of direct recordings of neural activity; this level of temporal resolution is necessary for measuring rapid cognitive processes, such as shifts of attention or information processing. In a handful of EEG studies, chemotherapy-related impairments have been documented in the so-called P300 EEG component[43-46], an electrophysiological correlate of information processing in working memory[64-66], suggesting that chemotherapy negatively affects the amount of attention resources available for stimulus processing. Together, MRI and EEG studies converge on the hypothesis that chemotherapy negatively affects neural structure and function within the fronto-parietal attention network.

In summary, chemotherapy negatively affects performance on behavioral measures of processing speed, attention, and memory, and has a profound impact on the structural and functional integrity of cortical regions within the fronto-parietal attention network. In the current proposal, our goal is to take a top-down approach to understanding how chemotherapy leads to impaired attention mechanisms. To this end, we will be employing a battery of cognitive (SA1) and simulated real world (SA3) tasks that target specific attention mechanisms; these tasks are able to measure subtle differences in attention processes within and between subjects on the order of milliseconds. To track task-related neural activity on the same timescale, we will incorporate EEG recordings into our cognitive battery (SA2) to link neural impairments of attention with cognitive impairments of attention in chemotherapy patients. Results from this line of research will provide motivation for further top-down research and new lines of bottom-up research to better understand how chemotherapy negatively affects the biological pathways underlying the fronto-parietal attention network.

Motivation

Despite numerous investigations on the impact of chemotherapy on cognitive performance, current research is limited in four major ways:

First, most research has studied breast cancer patients, making it difficult to dissociate the impact of chemotherapy on neurocognitive dysfunction from other factors specific to the breast cancer population. In particular, breast cancer almost exclusively affects female populations and impacts organs integral to female identity. Additionally, the lack of studies examining interactions between hormone treatment and chemotherapy treatment on cognitive health leaves hormonal factors as an alternative explanation for cognitive impairment observed in this population. In order to fully demonstrate the direct impact of chemotherapy on cognitive function, it is necessary to study chemotherapy-related cognitive decline in a broader cancer population that controls for gender, psychosocial, and hormonal confounds.

Second, the neural mechanisms of chemotherapy-related cognitive impairment remain largely unknown. Neuroimaging studies of chemobrain have examined blood-oxygenated level dependent activity associated with neural metabolic demands, and have converged on the hypothesis that chemotherapy affects the structural and functional integrity of frontal and parietal cortical regions. While these studies appear to provide some insight into the mechanisms of chemobrain, neuroimaging methods are limited both by their poor temporal resolution and reliance on blood-related correlates of neural activity. Given that chemotherapy introduces cardiotoxic effects and impairs the integrity of the blood brain barrier[67-69], current evidence is confounded by neuroimaging methods because they measure blood-related activity. Thus, neuroimaging studies remain inconclusive in determining whether chemotherapy affects the function of frontal and parietal cortical areas or the vasculature providing metabolic demands to frontal and parietal regions. To rule out vasculature-related impairments associated with chemotherapy, alternative methods

that more directly measure neural activity, such as scalp EEG, should be incorporated into studies of chemobrain. Currently, only a handful of electrophysiological studies have examined the impact of chemotherapy treatment on a single electrophysiological component (i.e. P300), which was evoked by a non-demanding cognitive task. Further electrophysiological studies must incorporate more demanding tasks that challenge specific attention mechanisms. Given the limitations of current research on the neural mechanisms of chemobrain, it is still unclear how chemotherapy affects the functional integrity of the fronto-parietal attention network. Together, cognitive and electrophysiological measures of attention provide a powerful tool for isolating neural mechanisms influenced by chemotherapy treatment. Thus, more work should be devoted to more rigorous and targeted electrophysiological studies of attention, which will be integral to separating neural from non-neural factors associated with chemobrain.

Third, neuropsychological tests typically recruit multiple cognitive domains, limiting specificity of impaired cognitive functions. For example, most paper-and-pencil tests recruit additional speed of processing and motor control abilities during task performance. Furthermore, methods for measuring task-related neural activity during neuropsychological testing are yet to be established. In contrast, computer-based cognitive tests allow researchers to selectively measure specific cognitive processes by manipulating display timing and stimulus characteristics, thus providing insight into how different cognitive systems interact during task performance. Furthermore, numerous studies have linked performance in computer-based cognitive tasks with neural function through MRI and EEG methods. In particular, the high temporal resolution of EEG methods demands cognitive testing instruments that provide concurrent temporal resolution through precisely timed stimulus presentation. Thus, studies of chemotherapy-related cognitive impairment would benefit from the incorporation of more sophisticated cognitive batteries.

Finally, previous studies have used measures with high experimental control and low external validity, providing limited insight into how chemotherapy-related cognitive impairment translates to real-world behavior. It is essential to understand how chemotherapy affects real-world behaviors that could have a profound impact on public health, as impairments in these activities could lead to incursions with the general population. Importantly, identifying which aspects of real-world behaviors are affected by chemotherapy could lead to the development of targeted rehabilitation strategies, ultimately leading to improved cognitive health and quality of life. Thus, combining basic and translational research into future studies will provide better insights into how the lives of chemotherapy patients – and the lives of those in their surroundings – are affected on a daily basis.

Section 3.0 Eligibility Criteria:

Inclusion criteria for HM patients include: 1) HM diagnosis, 2) scheduled to receive treatment based on risk classification, 3) between 19 to 80 years of age, and 4) normal or corrected-to-normal vision. Inclusion criteria for healthy controls will be that they are matched to patient demographics.

Exclusion criteria for HM patients include the presence of: 1) second cancer diagnosis in addition to recent HM diagnosis (however, patients with localized skin cancer may not be excluded), 2) prior radiation or chemotherapy treatment, 3) cognitive impairment (MMSE score <25) prior to baseline assessment, 4) patients who are critically ill or require urgent initiation of chemotherapy will be excluded from this study, 5) patients with any other condition that may not allow safe participation in the study based on the clinical judgment of the treating oncologist will be excluded. Exclusion criteria for healthy controls include HM cancer diagnosis in addition to all exclusion criteria for HM patients. There is the potential to detect cognitive impairment in research participants during cognitive assessment. After consent, if a participant receives an MMSE score of 20 or less, they will be discontinued from the study.

Section 4.0 Registration Procedure:

Patients will be recruited through the Department of Internal Medicine, Division of Hematology-Oncology with the assistance of Drs. Vijaya Bhatt, Lori Maness, Krishna Gundabolu, Sarah Holstein, Matthew Lunning, James Armitage, Muhamed Baljevic, Philip Bierman, Robert Bociek, and Julie Vose. Recently diagnosed HM patients will contact – or be contacted by – new patient coordinators to schedule a clinical visit at UNMC. During initial scheduling with new patient coordinators, patient contact information will be recorded in a Patient Tracker, and they will be informed that research is being conducted to study cognitive abilities in HM patients. A brief description of the study will be included in their new patient packet. At the time of their clinical visit, Drs. Bhatt, Maness, Gundabolu, Holstein, Lunning, James Armitage, Muhamed Baljevic, Philip Bierman, Robert Bociek, and Julie Voss will provide further information about the study, and ask patients if they are interested in participating. Interested patients will be screened for inclusion/exclusion criteria, provided with informed consent during their clinical visit, and their demographic information will be collected after consenting to participating in the study. After their clinical visit, a member of the Mind & Brain Health Laboratory (MBHL) will contact consented patients to schedule their initial pre- treatment research study visit. MBHL lab personnel will coordinate with patient case managers to determine their next treatment date so that subsequent study visits can be scheduled accordingly.

Demographically matched healthy controls will be recruited from the MBHL registry and RedCap (#564-10-EP: Building UNMC-based research programs focused on wellness, frailty, and aging) registry based on demographic information collected from HM patients who have already been inducted into the study. Specifically, healthy controls will be matched to HM patients along the dimensions of age ($\pm$5 years), gender (same gender), race (same race), and education ($\pm$2 years). These registries provide query options for search for specific demographic factors, and are comprised of individuals who have expressed interest in participating in research studies. In addition, spouses or caregivers of chemotherapy patients may be recruited as healthy controls to examine the psychosocial effects of caring for chemotherapy patients on cognitive abilities.

Given the limited availability for enrollment of HM patients into this study, potential research patients will not be selected based on demographic factors of gender and race. Nevertheless, equal preference will be given to individuals across all gender and race categories.

Research participants that have been recruited into the study will be undergo study induction either in the Division of Hematology/Oncology (HM patients) or in the Mind and Brain Health Labs (healthy controls). After study induction, all research participants will undergo the same testing battery within the Department of Neurological Sciences at each study visit. HM patients will complete each testing battery prior to undergoing their chemotherapy treatment scheduled on the same day.

Research participants will receive monetary compensation ($20/hour) for their participation. In the event that adequate funding is not secured for compensation, research participants will be recruited as volunteers.

Section 5.0 Treatment Plan of Research Design:

Experimental Design

Patients will be recruited from one of two targeted treatment groups, based on their risk stratification: 1) high risk group for examining the influence of chemotherapy on cognitive impairment; and 2) low risk supportive care treatment schedules, which represents the chemotherapy control group. Additionally, we will recruit a demographically matched (matched at age, gender, and educational status) healthy control group, which will serve as the cancer and chemotherapy control group.

Participants will complete a three-month longitudinal study that will examine the parametric effects of HM-specific chemotherapy treatments on cognitive and electrophysiological measures of attention

mechanisms. We will sample during intervals corresponding to the onset of treatment cycles, thus giving us the opportunity to examine additive dose-response effects of chemotherapy treatment. Sampling intervals for chemotherapy patients (or control patients) will occur according to the following schedule: 1) after HM diagnosis but prior to receiving chemotherapy treatment, providing a baseline assessment, 2) one month after baseline assessment **or after one treatment cycle (whichever comes first)**, 3) three months after baseline assessment **after three treatment cycles (whichever comes first)**.

Experimental Control Measures. There are several health factors that may be affected by HM disease and treatment that could potentially impact cognitive performance independent of chemotherapy treatment per se. To mitigate these potential confounds, we will measure these factors across patients and controls to include as cofactors during the modeling procedure of our analysis. If there is a link between factors unrelated to chemotherapy and variability in cognitive performance across groups, we will include these additional cofactors in the final model to control for these confounds; if there is no link between factors unrelated to chemotherapy and variability in cognitive performance, we will not include these factors in the final model.

Experimental control measures will include:

- Disease Comorbidity. Patients may have other diseases in addition to the HM diagnosis critical to the current proposal. Hematopoietic cell transplantation-comorbidity index (HCT-CI) is a tool commonly utilized in the transplant setting that measures multiple organ impairments across 17 different categories of organ dysfunction. Results from the HCT-CI are summated into a single total score, which will serve as a baseline measurement of disease comorbidity. Patients without any known or suspected cardiac or pulmonary diseases will be considered to have normal echocardiogram and pulmonary function test during calculation of HCT-CI.
- Anemia. HM patients will likely suffer from anemia that could result in fatigue. To control for anemia-related fatigue on cognitive ability, we will measure blood cell counts in patients and control participants. Blood cell counts will be collected from HM patients' most recent clinical visits. For healthy controls, we will obtain blood cell counts from their most recent clinical visit as well, though this measure may not be as recent as that of an HM patient; given that we do not anticipate these levels changing significantly in the healthy population, larger variability in the difference between blood and cognitive testing will not impose any limitation on our experimental design.
- Health and Mobility Questionnaires. Several questionnaires will be used to determine health, mobility, psychosocial status, and medication usage; these measures will be used to control for non-neural factors that may contribute to cognitive health. Questionnaires to be administered include: *Beck Depression Inventory* (depression screen), *medication usage form* (list of current medications), *health survey questionnaire* (inventory of health status and activity level), and *life space questionnaire* (mobility inventory).

Attention Battery

The goal of Specific Aim 1 is to construct a cognitive battery that decomposes the general construct of attention into its underlying mechanisms, enabling the examination of chemotherapy-related impairments across multiple processes of attention. To this end, we selected tasks that isolate four mechanisms of attention: 1) *processing speed* – time required to attend and recognize an item, 2) *inhibitory control* – ability to ignore irrelevant items, 3) *disengagement speed* – time required to release attention from an item, and 4) *storage capacity* – number of items that can be simultaneously attended.

Attention mechanisms measured by our battery are relevant to daily activities in the real world, such as holding a conversation in a noisy diner. For example, while listening to a friend speaking (i.e. target stimulus), the sounds of other patrons speaking (i.e. irrelevant stimulus) or dishes crashing to the floor (i.e.

distractor stimulus) compete for our limited attentional resources, thus providing opportunities for our attention to be distracted away from our friend speaking and towards an irrelevant stimulus. This hypothetical scenario provides examples of the four attention mechanisms measured in Specific Aim 1: speed at which speech of friend can be processed to understanding (*processing speed*), ability to ignore other patrons speaking and dishes crashing (*inhibitory control*), speed at which attention can be released from a distracting stimulus and re-engaged with the conversation (*disengagement speed*), and how much information from the conversation can be held in memory (*storage capacity*).

Collectively, our cognitive battery will offer millisecond-by-millisecond resolution of attention processes engaged by participants during task performance.

Capture task. Capture tasks[70-74] are an ideal candidate for studying attention because they offer experimenters a tool to precisely measure the *cost of processing an irrelevant stimulus* within a capturing display (*inhibitory control* mechanism) and the *timecourse of releasing attention* when it is captured by an irrelevant stimulus (*disengagement speed* mechanism).

In this task (Figure 2), participants are instructed to identify a target item (e.g. a green square with a notch on one side) presented among multiple distractor items within a search display; prior to the search display, a brief capture display is presented that contains a colored distractor item similar (contingent condition) or dissimilar (singleton condition) to the target color. Performance is measured as response time to correctly identify and respond with the location of the notch in target items. Previous studies have demonstrated: 1) longer reaction times in the contingent condition relative to the singleton condition, because attention is more likely to be distracted by a contingent stimulus that matches the target stimulus color, and 2) shorter reaction times in both conditions at longer inter-stimulus intervals (ISI; time difference between capture display and search display), because attention is more likely to disengage from the capturing stimulus prior to the onset of the search display when ISIs are longer.

In the current proposal, we will be able to directly measure the effects of chemotherapy treatment on inhibitory control mechanisms as they apply to the suppression of an irrelevant stimulus and disengagement mechanisms as they apply to the release of captured attention from an irrelevant stimulus.

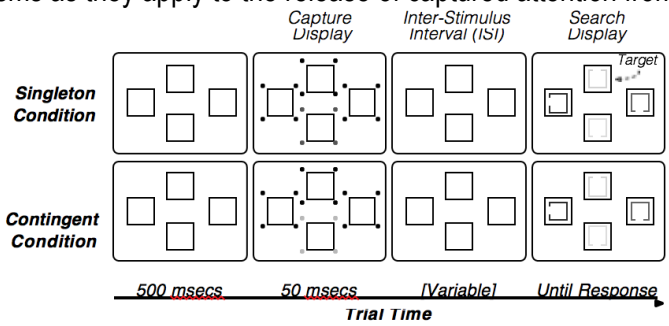


Figure 2: Capture Task Schematic

Filtering task. Filtering tasks[75,76] are an ideal candidate for studying attention because they offer experimenters a tool to precisely measure the *amount of information* that can be simultaneously attended (*storage capacity* mechanism) and the efficiency to *filter out irrelevant information* embedded among relevant information (*inhibitory control* mechanism).

In this task (Figure 3), participants are instructed to remember the value (e.g. orientation) of target items (e.g. blue lines) during a blank delay period (storage condition); on some trials, participants are instructed to ignore distractor items (e.g. red lines) presented simultaneously among target items (filtering condition). Performance is measured as response accuracy of correctly reporting the presence or absence of a target value change in a memory probe following the blank delay period. Previous studies have

demonstrated: 1) lower response accuracy as the number of relevant items to be remembered increases, 2) lower response accuracy in filtering conditions relative to storage conditions when the number of relevant items is held constant across conditions, and 3) individuals with larger storage capacities show smaller costs in response accuracy in the filtering condition.

In the current proposal, we will be able to directly measure the effects of chemotherapy treatment on storage capacity mechanisms as they apply to the amount of information that can remembered and inhibitory control mechanisms as they apply to the suppression of irrelevant information.

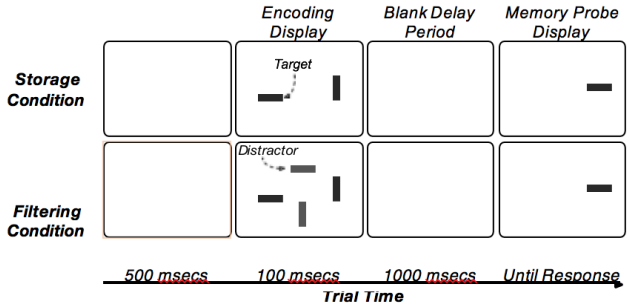


Figure 3: Filtering Task Schematic

Mobile cognitive testing. To track the timecourse of cognitive impairment between chemotherapy treatment cycles, patients will be given the option to complete customized attention tasks at home using BrainBaseline (Digital Artefacts), a mobile cognitive testing platform for use on a personal iPad or iPhone. De-identified data will be wirelessly transferred to HIPAA compliant servers maintained by Digital Artefacts.

Electrophysiology

The goal of Specific Aim 2 is to measure scalp electrophysiology to examine chemotherapy-related impairments in the neural mechanisms of attention on the timescale of milliseconds. To this end, we selected electrophysiological components that isolate four specific attention mechanisms: 1) *deployment speed* – time required to rapidly shift attention from one location to another, 2) *target enhancement* – amount of neural resources allocated towards selection of target item, 3) *distractor suppression* – amount of neural resources allocated towards inhibition of distractor item, and 4) *online storage* – amount of resources allocated toward storing target items in mind.

N2pc. The N2pc component[77-80] has been used in multiple empirical studies to examine neural mechanisms of attention because it reveals both when and where attention is being deployed early during visual processing. The N2pc is a relative negative amplitude deflection in posterior parietal electrodes with latency of 175-250 milliseconds, with more negative amplitudes occurring in electrodes contralateral to the attended visual field (Figure 4 left panel). For example, when attention must be deployed towards a target stimulus (e.g. a blue square outline with a notch on one side) presented in the left visual field, electrophysiological amplitudes observed in posterior parietal electrodes are more negative in contralateral (i.e. right hemisphere) electrodes relative to ipsilateral (i.e. left hemisphere) electrodes during the N2pc time window.

N2pc *latency* tracks *deployment speed*, where longer latencies suggest slower deployment speed; N2pc *amplitude* tracks *target enhancement,* where larger amplitudes suggest more resources were allocated towards target selection. Here, the N2pc component will be used to measure chemotherapy-related differences in target selection during capture and filtering tasks.

Pd. The Pd component[81-83] was more recently discovered and has been used to study inhibitory control mechanisms of attention due to its sensitivity to ignoring irrelevant information. The Pd is a relative

positive amplitude deflection in posterior electrodes with latency of 200-300 milliseconds, with more positive amplitudes occurring in electrodes contralateral to an ignored visual field (Figure 4 middle panel).

Pd *latency* tracks *deployment speed*, where longer latencies suggest slower deployment speed; Pd *amplitude* tracks *distractor suppression,* where larger amplitudes suggest more resources were allocated towards inhibiting distractor items. Here, the Pd component will be used to measure chemotherapy-related differences in distractor suppression during the capture task.

Contralateral Delay Activity (CDA). The CDA component has been used in multiple empirical studies to examine neural mechanisms of attention specific to storage capacity because it tracks both which information is being stored in mind and how much information is being stored in mind [75,76,84]. The CDA component is a sustained relative negative amplitude modulation in posterior electrodes that onsets at approximately 300-400 milliseconds, with more negative amplitudes occurring in electrodes contralateral to the remembered visual field (Figure 4 right panel). CDA *amplitude* tracks online storage, where larger amplitudes suggest that more items are stored in mind[75,76]. Here, the CDA will be used to measure chemotherapy-related differences in storage capacity during the filtering task.

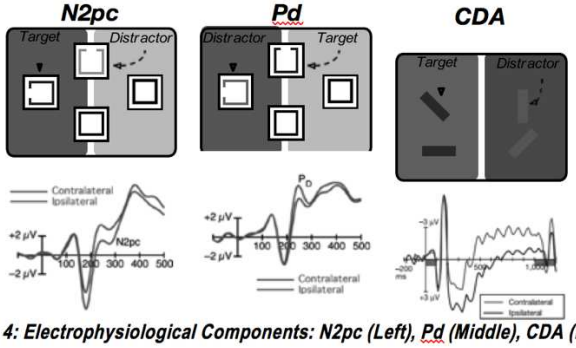


Figure 4: Electrophysiological Components: N2pc (Left), Pd (Middle), CDA (Right)

Driving Simulation

The goal of Specific Aim 3 is to implement simulations of driving scenarios that integrate laboratory-based attention mechanisms into a naturalistic environment that requires the coordination of multiple cognitive domains, including attention. By selectively challenging distinct attention mechanisms under different driving conditions and loads (e.g. traffic, pedestrians, road signs), we will be able to evaluate how impairments in attention affects driving outcomes. Broadly speaking, the goal of testing patients in simulated driving scenarios is to determine how computer-based cognitive tasks (SA1) translate into real-world driving behavior.

Car following task. The car following task requires drivers to follow a lead vehicle at a constant distance of two car lengths[85,86]. During this task, the lead vehicle pseudo-randomly changes its velocity, requiring drivers to vigilantly attend the lead vehicle to avoid an incursion while maintaining the instructed two-car length distance. Critically, the lead vehicle will occasionally brake during the drive, requiring drivers to rapidly brake in order to avoid collision. If attention is not fixed on the lead vehicle, an accident will likely occur. Outcome measures for the car following task include: 1) *mean distance* between lead vehicle and driver, 2) *brake delay*, measured as the delay between lead vehicle and driver braking time, and 3) *crash*, a binary variable that indicates if a collision occurred.

The car following task requires the recruitment of the following attention mechanisms: 1) *processing speed*, used to process and update working memory with task-specific cues (e.g. braking, change of speed) provided by the lead vehicle, 2) *target enhancement,* required to enhance task-specific lead vehicle cues, and 3) *inhibitory control,* required to inhibit the processing of irrelevant environmental information (e.g. other vehicles, pedestrians, etc.).

Visual search task. The visual search task[87-91] requires participants to search for a target item among multiple distractor items while driving; this task uses displays similar to the search display of the capture task. Search item configurations can be manipulated to evoke either the N2pc or the Pd to measure attentional shifts related to target enhancement or distractor suppression, respectively, during driving performance. This line of research will be the first to examine rapid shifts of attention during driving behavior.

The visual search task requires the recruitment of the following attention mechanisms: 1) *processing speed,* used to process each search item in turn in order to find the target item, 2) *deployment speed,* used to rapidly shift attention towards candidate search items, and 3) *target enhancement,* used to resolve target items from distractor items.

	Specific Aim 1		**Specific Aim 2**			**Specific Aim 3**	
Attention Mechanism	*Capture Task*	*Filtering Task*	*N2pc*	*Pd*	*CDA*	*Car Following*	*Visual Search*
Processing Speed	**X**					**X**	**X**
Deployment Speed			**X**	**X**			**X**
Target Enhancement			**X**			**X**	**X**
Distractor Suppression				**X**			
Inhibitory Control	**X**	**X**			**X**	**X**	
Disengagement Speed	**X**						
Storage Capacity		**X**			**X**		

Table 2: Summary of attention mechanisms probed in each specific aim Auxiliary Measurements

In addition to the proposed battery, we will administer several neuropsychological exams to determine whether the range of cognitive impairments predominately observed in the breast cancer population are reflected in the HM population. These exams will give us the opportunity to link patterns of cognitive impairment between cancer **populations**. Additionally, we have selected novel measures (circulating inflammatory proteins, retinal anatomy) within the domain of the chemobrain literature to further explore the impact of chemotherapy on the brain and body.

Cognitive assessment. Clinical neuropsychological exams to be used in the current proposal include: *Mini-Mental State Examination*[5,14,20] (MMSE; mental status, dementia screening tool), *Trails A and B*[1-4,6-11,15,18,20,22-24,35] (processing speed), *Useful Field of View* (UFOV; processing speed, divided attention, inhibitory control), *Paced Auditory Serial Attention Task*[18,23] (PASAT; working memory, arithmetic), *Stroop*[2,3,5-9,12,17,23,24] (executive function).

Vision assessment. Clinical measures of visual deficits to be used include: *visual acuity*, *contrast sensitivity* (discrimination threshold for light and dark boundaries), *frequency doubler task* (visual field deficits), *visual function questionnaire* (self-reported impairment of visual function), and *neuro-ophthalmology supplement (NAS)-10* (self-reported impairment of visual function).

Retinal anatomy. Retinal anatomy is an underutilized tool for studying the link between brain disease and cognitive impairment, particularly in cancer populations. Optical coherence tomography (OCT) provides an easy, non-invasive and reliable method of studying retinal anatomy in healthy and diseased populations. With an axial resolution of 4-6 micrometer, the new generation spectral domain OCT can reliably identify the various neuronal layers of the retina.

Previous work has demonstrated a link between retinal anatomy integrity and neurodegeneration[110], particularly in Alzheimer's Disease[111], Parkinson's Disease[112], and Multiple Sclerosis[113]. In the current proposal, OCT measurements will allow us to determine the presence of neurodegeneration of the retina in cancer patients receiving chemotherapy, and link declines in retinal anatomy integrity with concurrent declines in cognitive performance. Thus, this method has potential to further develop non-invasive and rapid imaging biomarkers for chemotherapy-related cognitive impairment.

Cirrus HD-OCT (Carl Zeiss Meditec Inc.) will be used to obtain scans of the retina and optic nerve. Specifically, the Macular Cube and the Optic disc cube scans will be performed at each visit. These scans can be performed without the need for pupillary dilation and takes about 2 minutes per eye. The relevant parameters obtained with the optic nerve scan includes the *retinal nerve fiber layer thickness* (global average, quadrant average and clock hour average). The macular cube scans will provide the *ganglion cell/inner plexiform layer thickness* (global average and sector average) and *macular thickness*.

Given the link between retinal anatomy and neurodegeneration, which has direct implications for cognitive impairment, OCT will be measured for all three groups across the three study visits in the following manner: HM groups will undergo OCT measurement at all three study visits; given that we anticipate minimal variability in healthy participants across a three-month time period, a randomly sampled subset of healthy controls (n=10) will undergo OCT across all three study visits. This measurement protocol will allow us to control for any within-subject variability in retinal anatomy that may be observed across groups so that we can account for concurrent variability in cognitive performance.

Circulatory Inflammatory Proteins. Circulatory levels of cytokine interleukin (IL) proteins and C-Reactive Proteins (CRPs) have been found to negatively affect brain function. Specifically, increased levels of IL proteins[92-97] and CRPs[116-118] have both been associated with impairments of memory and executive function, and has been implicated as a potential mechanism for chemotherapy-related cognitive impairment[114,115]. Given tumor presence and chemotherapy treatment associated with increased levels of these proteins in the blood[98-100], measurement of inflammatory protein levels is essential to further understand the link between cancer, chemotherapy, and cognitive impairment.

Given the link between inflammatory protein concentration levels and cognitive impairment, CRP concentrations will be measured for all three groups at all three study visits; this measurement protocol will allow us to control for any within-subject variability in CRP concentration levels that may be observed across groups so that we can account for concurrent variability in cognitive performance.

Section 6.0 Measurement of Effect:

Cognitive Battery

- Response time (Capture Task) and response accuracy (Filtering Task)

Electrophysiology

- Amplitude and latency of N2pc, Pd, and CDA electrophysiological components

Driving Simulation

- Response time (Visual Search Task)
- Brake time, mean following distance, and number of incursions (Car Following Task)

CRP

- Concentration levels of circulating inflammatory proteins

OCT

- Surface area and volume of retinal ganglion cell layer and optic nerve fiber

Given that we are not proposing an intervention trial our primary outcome measures will not be related to the progression of HM.

Section 7.0 Study Parameters:

Summary of Study Events and Durations. Each study visit is anticipated to take approximately 2.5 hours to complete. Table 1 contains a summary for the schedule of study events to occur at each research component. Study induction takes place at the beginning of Visit 1. Time requirements for research participants at each study event are as follows:

- *Study Induction (~.5 total hours)*:
  - Informed consent (20 minutes)
  - Demographic Information (10 minutes)
  - Comorbidity Index (conducted offline)
  - Anemia Evaluation (conducted offline
- *Each Study Visit (~2.5 total hours):*
  - Cognitive Battery (40 minutes)
  - Electrophysiology (15 minutes)
  - Driving Simulation (20 minutes)
  - Neuropsychological Exams (45 minutes)
  - Health & Mobility Questionnaires (10 minutes)
  - OCT (10 minutes)
  - Blood Collection (10 minutes)

	Pre-Induction	**Study Induction**	**Visit 1 (Month 0)**	**Visit 2 (After Month 1 or 1 treatment cycle)**	**Visit 3 (After Month 3 or 3 treatment cycles)**
HM Diagnosis	**X**				
Control Group ID	**X**				
Informed Consent		**X**			
Demographic Information		**X**			
Comorbidity Index		**X**			
Anemia Evaluation		**X**			
Chemotherapy Treatment			**X**	**X**	**X**
Cognitive Battery			**X**	**X**	**X**
Electrophysiology			**X**	**X**	**X**
Driving Simulation			**X**	**X**	**X**
Neuropsychological Exams			**X**	**X**	**X**
Health & Mobility Questionnaires			**X**	**X**	**X**

OCT			**X**	**X**	**X**
Blood Collection/ Protein Assay			**X**	**X**	**X**

Section 8.0 Drug Formulation and Procurement:
This pilot study is not a pharmaceutical trial.

Section 9.0 Toxicity and Adverse Event Reporting Guidelines:
This research has been classified as Minimal Risk.

There is the potential to detect cognitive impairment in research participants during cognitive assessment. After consent, if a participant receives an MMSE score of 20 or less, they will be discontinued from the study. If cognitive impairment is identified, research personnel will proceed in the following way. First, the participant will be informed that an unexpected finding was encountered that may have clinical significance, and that the clinical significance is best determined in conjunction with his or her primary care physician. Next, research personnel will ask the participant for their permission to contact their primary care physician to help facilitate follow-up to determine clinical significance. The primary care physician will then be contacted and provided clinical context and concerns sufficient to allow for subsequent evaluation, workup, and treatment of any unexpected finding. If the participant refuses to have the research personnel directly contact their physician, the research personnel will offer the participant a written explanation that an abnormal neurological finding was encountered and the written material will include encouragement to have an evaluation, as well as a phone number of the Mind and Brain Health Labs to contact with questions or in case they change their mind.

Section 10.0 Statistical Considerations:

Our primary goal is to examine the effects of chemotherapy on behavioral and electrophysiological measures of cognitive ability in an understudied cancer population. To this end, analyses for the proposed pilot project will be performed on three groups: healthy controls (no cancer, no chemotherapy), very-low to intermediate risk HM patients receiving supportive care treatment (no chemotherapy), and intermediate to very-high risk HM patients receiving chemotherapy treatment.

Statistical Power. Although many of the statistical analyses will involve complex modeling procedures, the main emphasis of our aims and hypotheses is to determine differences between groups and pre-post treatment. Hence, the issue of statistical power can be addressed via consideration of the magnitude of standardized effect sizes that can be detected with reasonable probability. The current study aims to collect pilot data and demonstrate protocol feasibility for future studies and funding opportunities. As such, we plan to obtain 15 samples per group for a total sample size of 45.

While we realize we will not have sufficient power to declare smaller effects statistically significant, as this is a pilot study, it will allow us to estimate effect sizes for a number of outcomes to conduct fully powered studies. In future large-scale confirmatory studies, with a sample size of 32 per group, we will have 80% power to detect a standardized effect size of 0.65 (a medium to large effect) for within group changes, and an effect size of .9 for between group differences. These power calculations assume a two-tailed alpha of 0.01 to informally adjust for multiple comparisons and multiple testing. A standardized effect size of 0.65 corresponds to a 10% difference in response time from healthy controls (mean=1394.75, standard deviation = 213.23). This sample size will allow adequate power to detect medium to large effects within group, and large effects between groups.

Statistical Analysis. To assess the data collected, for each group, we will first produce frequency tables, calculate descriptive statistics, and create univariate graphs (e.g. box-plots, histograms) on the

predictor and response variables to investigate distributional properties and check for outliers in the data. Although the specific statistical models that we will use to test our formal hypotheses and to calculate confidence intervals will depend on the outcome distributions that we observe in our data, we anticipate using linear mixed models and generalized linear mixed models, as appropriate. This modeling approach allows us to properly account for the distribution of the outcome measure while also properly modeling repeated effects and adjusting for potentially confounding variables. Confidence intervals of all effects will be calculated in order to assess clinical significance of statistical results.

We will employ linear mixed models and general linear models to **assess** within-subject, between-subject, and mixed effects of:

- Behavior:
  - Capture condition, stimulus ISI, and treatment group on response time measures in the Capture Task
  - Filtering condition, storage load, and treatment group on response accuracy measures in the Filtering Task
- Driving simulation:
  - Treatment group on response time measures in the Visual Search Task
  - Treatment group on lead car distance variability, brake time, and number of incursions during the Car Following Task
- Electrophysiology:
  - Capture condition, stimulus ISI, and treatment group on Pd (amplitude, latency) and N2pc (amplitude, latency) measures during the Capture Task of the Attention Battery
  - Filtering condition, storage load, and treatment group on N2pc (amplitude, latency) and CDA (amplitude) measures during the Filtering Task of the Attention Battery
  - Treatment group on N2pc (amplitude, latency) and Pd (amplitude, latency) measures during the Visual Search Task of the Driving Simulation

Our primary hypothesis is that chemotherapy treatment negatively affects core neural mechanisms of attention. Here, we present predictions for how chemotherapy would affect outcome measures from each task and electrophysiological measure, where specific predictions are given based on how impairments in different attention mechanisms would affect the pattern of data observed in each task.

Attention Measures

Capture task. Two dissociable mechanisms of attention are measured in this task. First, *inhibitory control* is required to suppress the processing of the capture display; inhibitory control mechanisms will be tracked by the Pd component. Second, *disengagement speed* is required to rapidly release attention from capture displays to prepare for the subsequent search display; disengagement mechanisms will be tracked by the N2pc component. There are three possible predictions for impairments in each attention measured in the capture task.

- *Hypothesis 1: Inhibition effect/No disengagement effect*. Relative to comparison subjects, this hypothesis predicts a chemotherapy-related: 1) increase in response time differences between contingent and singleton capture conditions, 2) increase in Pd amplitude, and 3) decrease in N2pc amplitude.
- *Hypothesis 2: No inhibition effect, disengagement effect*. Relative to comparison subjects, this hypothesis predicts a chemotherapy-related: 1) increase in response times in both capture conditions, 2) decrease in N2pc amplitude, and 3) no difference in Pd amplitude.

- *Hypothesis 3: Inhibition effect, disengagement effect*. Relative to comparison subjects, this hypothesis predicts a chemotherapy-related: 1) increase in response times in both capture conditions, 2) increase in response time differences between contingent and singleton capture conditions, 3) increase in Pd amplitude, and 4) decrease in N2pc amplitude.

Filtering task. Two dissociable mechanisms of attention are measured in this task. First, *inhibitory control* is required to suppress the encoding of distractor items; inhibitory control mechanisms will be tracked by both the N2pc and CDA electrophysiological components. Second, sufficient *storage capacity* is required to maintain multiple items in working memory during the delay period; storage capacity will be tracked by the CDA electrophysiological component. There are three possible predictions for impairments in each attention mechanism measured in the filtering task.

- *Hypothesis 1: Capacity effect, no inhibitory control effect*. Relative to comparison subjects, this hypothesis predicts a chemotherapy-related: 1) decrease in response accuracy in both storage and filtering conditions, 2) decrease in CDA amplitude, and 3) no difference in N2pc amplitude.
- *Hypothesis 2: No capacity effect, inhibitory control effect*. Relative to comparison subjects, this hypothesis predicts a chemotherapy-related: 1) decrease in response accuracy only in the filter condition, 2) increase in N2pc amplitude, and 3) increase in CDA amplitude.
- *Hypothesis 3: Capacity effect, inhibitory control effect*. Relative to comparison subjects, this hypothesis predicts a chemotherapy-related: 1) increase in response accuracy differences between filtering and storage conditions, 2) increase in N2pc amplitude, and 3) increase in CDA amplitude.

Car following task. According to the hypothesis that chemotherapy treatment impairs *processing speed*, a chemotherapy-related decline should be observed in car-following performance because fewer resources would be available for processing lead vehicle events. Specifically, delayed processing would lead to delayed updating of lead vehicle driving information, which would lead to greater variability in car-driver distance and longer delay in driver brake onset, where longer brake delays would lead to more crashes.

Visual search task. According to the hypothesis that chemotherapy treatment impairs *deployment speed*, a chemotherapy-related increase in response time should be observed because attentional resources will be slower to deploy; furthermore, changes in the complexity of the driving environment (e.g. road hazards, high visual load) would lead to longer response times as a function of complexity because attentional resources would be more engaged with more complex environments, leading to poorer *inhibitory control*. For electrophysiology, this hypothesis predicts chemotherapy-related reductions in N2pc amplitude and increases in N2pc latency – because lower inhibitory control would lead to a lower probability of being prepared to deploy attention towards the task-relevant search display.

Auxiliary Measures

Cognitive assessment. According to the hypothesis that chemotherapy impairs attention mechanisms, we predict impairments in performance across neuropsychological exams within the cognitive assessment, because these tests measure cognitive abilities directly related to attention. For example, memory tests (e.g. CVLT, BVRT) require attention to successfully encode information into memory storage; failures of attention would lead to failures of encoding into memory, and thus impairments in memory retrieval.

Vision assessment and retinal anatomy. Our hypothesis is that chemotherapy negatively affects higher-level attention mechanisms, such that attention impairments cannot be explained by impairments in low-level visual processes. Therefore, we predict no changes across vision assessment exams and questionnaires. Conversely, given the hypothesis that chemotherapy leads to morphological changes in

neural structures, and the fact that the retina is a neural structure, we do predict reductions in retinal and optic nerve thickness.

C-Reactive Proteins. According to previous work, circulatory levels of C-Reactive Proteins (CRPs) increase in response to inflammation, including tumor genesis and growth. We therefore predict an increase in CRP levels in HM patients relative to healthy controls; furthermore, we predict further increase in CRP levels in HM patients receiving chemotherapy relative to HM patients receive best supportive care treatment. Finally, we hypothesis that increases in CRP levels will predict concurrent increases in attention impairment both within and between research participants.

Section 11.0 Records to be Kept:
The following forms will be collected during each study visit, and stored in locked filing cabinets within keycard restricted lab space in the Mind and Brain Health Labs (first floor of Clarkson Doctor Building North). Data collection forms will be entered electronically into a study database on a password-protected, encrypted, dedicated research network.

- Phone Screen Script
- Patient Tracker
- Demographic Form
- MMSE Data Collection Form
- HM Data Collection Form
- Hematopoietic Cell Transplant Co-Morbidity Index (HCT-CI)
- Beck Depression Index
- Life Space Questionnaire
- Medication Form
- Health Survey
- Visual Function Questionnaire
- Far Visual Acuity Form
- Contrast Sensitivity Form
- Frequency Doubler Task (FDT) Record Sheet
- Trails A Data Collection Form
- Trails B Data Collection Form
- Stroop Test – Participant Form
- Stroop Test – Scoring Form
- PASAT Scoring Sheet
- UFOV Scoring Sheet

In addition to the forms indicated above, electronic records of performance during the cognitive, electrophysiological, and simulation batteries will be maintained in their raw form on password protected computers. After completing each testing battery, raw data will be stored on a password-protected, encrypted, dedicated research network.

Section 12.0 Patient Consent: The consent form must adhere to the guidelines established by the Institutional Review Board of the University of Nebraska Medical Center.

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Section 14.0 Data Collection Forms:

Submitted as separate document