**Understanding Cancer-Related Cognitive Impairment: A Comprehensive Review**

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**Abstract**

Cancer-related cognitive impairment (CRCI), formerly ‘chemo-brain,’ is one added burden cancer patients and survivors face. This side effect is characterized by deficits in memory, attention, and executive function. The damage of cancer treatment, the cancer itself, and traits about the individual are all implicated as causes of CRCI. In the last twenty years, inflammation has been considered as a potential driving force in CRCI, either through direct effects or as a mediator between the other factors and cognition. Understanding how these components influence CRCI could enable researchers and healthcare professionals to develop informed interventions. Studies that can assess subtle changes in cognitive and biological factors will be a crucial next step for CRCI research.

**Understanding Cancer-Related Cognitive Impairment: A Comprehensive Review**

Cancer is a devastating disease that impacts an astounding number of people. According to the World Cancer Research Fund International (2023), there were 18.1 million new cancer cases diagnosed worldwide in 2020. The American Cancer Society estimated that 1,958,310 new cancer cases would be diagnosed in the United States throughout 2023, resulting in the United States being the second-highest contributor to worldwide cases (Siegel et al., 2023; World Cancer Research Fund International, 2023). To put this in more relatable terms, there is nearly a 40% chance of being diagnosed with an invasive type of cancer throughout a person’s lifetime (40.9% for men, 39.1% for women; Siegel et al., 2023). On a more positive note, cancer survivability has substantially improved over time. While the average 5-year survival rate for all cancers was 49% in the 1970s, the 5-year survival rate in the 2010s was 68% (Siegel et al., 2023). The American Cancer Society projected that if cancer mortality rates had remained constant from their spurious peak in 1991, there would have been 3,820,800 additional cancer deaths over the last two decades (Siegel et al., 2023). The advancements in screening diagnostics and cancer treatments have helped millions of people live to experience life after cancer. However, with this ever-growing number of people adjusting to life post-cancer diagnosis, a new need has arisen: how to improve patient and survivor quality of life. In addition to battling cancer, these individuals face a litany of side effects, including weight changes, fatigue, depression, anxiety, and cancer-related cognitive impairment (CRCI; Parada et al., 2023). This impairment, commonly referred to as “chemo-brain,” has become a focus of research in the last twenty years, due to the substantial impacts it can have on a patient’s life. In interviews, patients often describe forgetting common words or tasks, struggling with directions, and no longer being able to multitask (Wu et al., 2019). The ripple effect of these symptoms can grow immensely, as CRCI has been linked to loss of social relationships, medication nonadherence, and lower survival rates (Franco-Rocha et al, 2023). Parada et al. (2023) reported that up to 53% of cancer survivors experience cognitive difficulties when returning to school or work, which can add financial strain. CRCI can even become a safety concern, as Yuen et al. (2008) reported a possible association between CRCI and poorer driving performance. As the ramifications of these side effects of cancer have become more apparent and the number of people battling CRCI has grown, researchers have raced to understand this dysfunction.

While it has been well established that CRCI affects the cognitive domains of working memory, attention, and executive function, and to a lesser extent, psychomotor speed, visuospatial abilities, and verbal fluency, understanding the cause of CRCI has remained more elusive (Hermelink, 2015). Originally, CRCI was assumed to be a side effect of the neurotoxicity of chemotherapy, hence the moniker of “chemo-brain,” (Hermelink, 2015). However, as researchers shifted from cross-sectional designs to more longitudinal studies in the mid- and late-1990s, evidence began to build that CRCI was present before treatment was ever administered (Hermelink, 2015). Being able to determine a cause of CRCI has been further complicated by the difficulty of measuring this cognitive impairment. Occurrence rates of CRCI can range between 15% to 75%, depending on the study, with subjective and objective measures rarely correlating (Hermelink, 2015; Parada et al., 2023). In response to the difficulties presented by CRCI research, the Hurricane Voices Breast Cancer Foundation gathered 30 healthcare professionals and three patient advocates from around the world to attend a workshop in Banff, Canada on April 23, 2003 (Tannock et al., 2003). This conference, later referred to as the Banff Conference, became a major point of consolidation, with the components of this conference having a ripple effect through all future CRCI research. One such component was the introduction of the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) scale, with the modified version (FACT-Cog version 3), becoming the most commonly utilized self-report assessment of CRCI used to this day (Henneghan et al., 2021a; Tannock et al., 2003). A second, influential outcome of the Banff Conference was the comparison of CRCI to sickness behavior within the measurement components. At a smaller American CRCI workshop in 2001, researchers and clinicians had discussed the similarities between CRCI and the animal model of sickness behavior, which refers to a cluster of symptoms including gastrointestinal difficulties, pain, sleep disturbances, distress, and decreased environment exploration (Cleeland et al., 2003). Importantly, the sickness behavior model is well studied, with a strong understanding of the biological processes involved. The American representatives went on to share their previous findings at the Banff Conference, providing an avenue to assess biological mechanisms associated with sickness behavior while accounting for the CRCI measurement concerns raised by different teams. The consolidation of information at the Banff Conference took the field many steps forward, as researchers then dove into the many possible underlying causes of CRCI based on the animal model of sickness behavior. However, despite these steps forward, we still do not fully understand what is causing CRCI. As stated by Chae et al. (2016), “the lack of understanding of the biological mechanisms underpinning [CRCI] remains the major impediment to the development of effective management strategies”, (p. 10). Thus, the goal of the current paper is to elucidate the potential causes of CRCI, consider what component may underlay these causes, and discuss the measurement approaches that could facilitate CRCI research progress and intervention development.

**Contributing Factors**

One of the difficulties slowing progress in determining the underlying cause of CRCI is the vast array of factors contributing to this form of dysfunction. The list of postulated CRCI contributors includes the cancer treatment, the cancer itself, genetic susceptibility, traits of the patient, and mental health factors. While these components do not exist in a vacuum and likely interact, separately assessing how each factor contributes to cognitive dysfunction can elucidate the complexities of CRCI.

**The Damage of Cancer Treatment**

***The Pathways to Damage***

The direct neurotoxicity of cancer treatment has continued to be considered a major contributor to CRCI, with the potential routes to direct brain damage representing a large portion of CRCI research. As an immune-privileged site, the brain is heavily dependent on the tightly packed endothelial cells that make up the blood-brain barrier (BBB) to prevent the sensitive tissue from exposure to any toxic substances in the bloodstream (Russo & McGavern, 2015). While the BBB can block substances with a molecular weight of at least 500 daltons, smaller molecules can slip past (Myers et al., 2008). In addition, chemotherapeutic agents can damage the BBB, compromising the junctions and allowing neurotoxic agents to pass through and damage the cerebral parenchyma. Wardill et al. (2016) reported that after intravenous injection, the chemotherapy agents bis-chloroethyl nitrosourea (BCNU), paclitaxel, and 5-fluorouracil were detected within the cerebral parenchyma of rodents and primates, illustrating the susceptibility of the BBB, and the potential for direct neurotoxic effects. Additionally, chemotherapeutic and radiation agents can be extremely damaging to DNA. Ren et al. (2019) reported that in “80% of human cancers, the immortal phenotype of cancer cells is due to an increase in telomerase activity,” so many cancer treatments are designed to target this telomere-shortening enzyme (p. 1090). Unfortunately, these treatments cannot differentiate between a tumor cell and a healthy cell, leading to dysregulated telomere shortening in numerous cells (Ren et al., 2019). This damage to DNA then leads to apoptosis and cell death, even within the central nervous system (CNS; Ren et al., 2019). This neuronal death is reflected in structural changes, as magnetic resonance imaging (MRI) studies frequently report reduced volume in the hippocampus, an area crucial to learning and memory (Orchard et al., 2017). In a functional MRI (fMRI) study with oncology patients, Wang et al. (2016) found significantly reduced activation in the right dorsolateral prefrontal cortex during an n-back assessment for working memory, as compared to healthy controls. The authors also reported hypoactivation in the left hippocampus during a visual recognition task, building evidence that structural damage to areas related to memory could be contributing to CRCI (Wang et al., 2016). It is important to note, however, that the self-report measures they utilized (including FACT-Cog) were not significantly correlated with the neuroimaging results, further illustrating the difficulties in CRCI measurement.

In addition to directly damaging neural tissue, cancer treatments may also hinder the brain’s ability to restore itself by impairing neurogenesis. Though most neurons are non-dividing (in the adult brain), three special regions, the subgranular zone of the dentate gyrus of the hippocampus (the most important of the three), the stratum, and the subventricle zone of the lateral ventricles, exhibit neurogenesis, providing new neurons and supporting cells to recover from regular damage (Nguyen & Ehrlich, 2020). Thus, as cancer treatments are connected with hippocampal degradation, there is a possibility that neurogenesis is also impacted. Gibson and Monje (2021) acknowledged that impaired hippocampal neurogenesis has become a controversial potential cause of CRCI, as a baseline level of healthy neurogenesis has not been established. While the exact mechanisms and thresholds have yet to be determined, Nguyen & Ehrlich (2020) reported that a variety of common chemotherapy agents, including doxorubicin, paclitaxel, and cisplatin, were correlated with memory impairment and reductions in neurogenesis protein markers, such as BrdU and doublecortin. Similar results have been seen with reductions of brain-derived neurotrophic factor (BDNF), a growth factor that promotes neurogenesis, after treatment administration (Nguyen & Ehrlich, 2020; Yap et al., 2021). Future research may be able to delineate how cancer treatments can inhibit neurogenesis, prevent neuronal recovery, and impact CRCI.

A third route between cancer treatment and CRCI is the altering of the communication system in the brain. Gibson and Monje (2021) reported that cranial irradiation in rodents led to reductions in the length, density, and branching of hippocampal dendrites, and overall reductions in the number of spines. Nguyen and Ehrlich (2020) reported similar dendritic pruning in the cingulate after the administration of doxorubicin, fluorouracil, and cisplatin. On the other side of the synaptic cleft, neurotransmitters can be impacted as well. In a study on brain slices from mice treated with the chemotherapeutic agent carboplatin, Kaplan et al. (2016) reported that the uptake of both serotonin and dopamine was diminished, despite the lack of changes in reserve pool content, indicating that these neurotransmitters were not being released efficiently. In a third blow to transmission, treatments can also impact myelin plasticity, and hamper the maintenance of long-term potentiation (Mounier et al., 2020). Through the use of transmission electron microscopy, Geraghty et al. (2019) demonstrated a thinner myelin sheath in mice exposed to methotrexate chemotherapy than in healthy controls. In combination, chemotherapy can limit a neuron’s ability to send, carry, and receive a message, severely impacting cognition. In their study with mice trained to complete a 5-choice reaction time task, Huo et al. (2018) found that administration of cisplatin resulted in a reduction of synaptic integrity markers and an omission-related change in the percentage of correct responses. The authors proposed that by altering neurotransmission, chemotherapy can cause attention impairments, one of the key components of CRCI. While the heavy reliance on dissection techniques for this potential avenue presents a difficulty for human studies, the results from animal models raise the possibility that treatment-driven changes to neurotransmission may impact CRCI in humans.

***Treatment Regimen***

There is an incredibly wide variety of chemotherapeutic agents, all designed to target different components of cancer cells, opening the possibility of different impacts on cognition. Mounier et al. (2020) conducted a review on the types of chemotherapies and presented links to the associated cognitive impairments. Hormone therapies, such as tamoxifen, stop or alter the hormones central to certain cancers, such as breast, prostate, or endometrial cancer. Mounier et al. (2020) reported that tamoxifen was related to impaired retrieval functions in mice and impaired verbal fluency, memory, processing speed, and visuospatial functioning in humans. A second class of chemotherapy drugs, antimicrotubule agents, keep the cytoskeleton of the cell in one shape, preventing mitosis and proliferation. These drugs, including paclitaxel and docetaxel, have been a source of debate in CRCI research, as cognitive deficits are not always present (Mounier et al., 2020). In rats and mice, antimicrotubule agents have been associated with impaired rule learning and object recognition (Mounier et al., 2020). In human studies, paclitaxel has been related to behavior changes, hallucinations, and confusion (Mounier et al., 2020). Another class of chemotherapy drugs, alkylating agents, are designed to attach an alkyl group to the guanine base of DNA, keeping the cell from reproducing and leading to apoptotic cell death (Mounier et al., 2020). This class of agents, including cyclophosphamide, ThioTEPA, and oxaliplatin, was linked to impaired memory retention and novel object recognition in mice (Mounier et al., 2020). The class of chemotherapy agents known as antimetabolites masquerade as metabolites to trick cancer cells into using the slightly altered version of the DNA-building molecule, preventing any further replication. These drugs, including methotrexate and 5-fluorouracil, were associated with impaired memory (usually spatial memory) and learning in rats (Mounier et al., 2020). The final class of chemotherapy drugs, the DNA-breaking cytotoxic antibiotics, such as doxorubicin, have been known to impair avoidance conditioning in rats (Mounier et al., 2020). The direct effects of alkylating agents, antimetabolites, and cytotoxic antibiotics in humans are difficult to tell, as they are rarely used separately from other agents. While these combinations exhibit the same impairments in learning and memory established with the other treatments, they are also linked to impaired executive function (Mounier et al., 2020). Determining whether impaired executive control is caused by a specific chemotherapeutic drug or if it is a unique result of combining agents presents another avenue for future CRCI research.

An additional layer to understanding the impact of chemotherapy treatments on CRCI is introduced by the dosage and length of treatment. Myers et al. (2008) reported that while methotrexate is not associated with neurotoxicity at lower doses, higher doses can cross the BBB. The importance of dosage is not restricted to antimetabolites, as studies with the alkylating agent cisplatin have shown a relationship between dosage and the volume and speed of dendritic pruning (Gibson and Monje, 2021). As chemotherapy damage increases, so does impairment. In a study assessing mice over three time points, Tang et al. (2022) found that stronger doses of paclitaxel maintained cognitive dysfunction for longer periods of time. The accumulation of chemotherapy in the system is also important, as most treatments require multiple administrations or cycles. When evaluating breast cancer patients across multiple cycles, Durán-Gómez et al. (2022) found that the number of cycles was significantly related to the FACT-Cog subscales of Perceived Cognitive Impairment, Quality of Life, Perceived Cognitive Ability, and Comments from Others. Similarly, there was a significant inverse relationship between the number of cycles and scores on a phonological and semantic verbal fluency task (Durán-Gómez et al., 2022). It is worth noting that this study did find a significant correlation between FACT-Cog and the neuropsychological verbal fluency assessment (Durán-Gómez et al., 2022). While these studies on the impact of dosage on CRCI are still very new, they raise the possibility that dosage could be even more important than chemotherapy type.

While chemotherapy is a staple of cancer treatment, it is not the only regimen that impacts CRCI. As Nagtegaal et al. (2020) reported the thinning of cortical thickness depended on radiation dose, the dosage of radiation could be just as important as the dosage of chemotherapy. When assessing the effects of radiation dose and location on CRCI, Gan et al. (2011) found a significant correlation between radiation dose to the temporal lobes and memory encoding. The authors also reported a statistically significant correlation between radiation doses to the cerebellum and coordination scores on the Pegboard test (Gan et al, 2011). Interestingly, there was not a significant difference between the group who received only radiation and the group who received radiation and chemotherapy, illustrating that radiation alone is sufficient to induce CRCI (Gan et al, 2011). This raises the question of what other cancer treatment regimens could impact CRCI. For example, there is preliminary evidence that stem cell transplants can impact cognitive impairment, even for two years post-treatment (Harrison et al., 2021; Wu et al., 2019). Though research into the cognitive impacts of stem cell transplants is still in its infancy, these early correlations illustrate that there is a wider variety of cancer treatment regimens that could impact CRCI.

**The Impact of Having Cancer**

Challenging the original expectations that CRCI was solely driven by chemotherapy, longitudinal studies of the 1990s began illustrating that CRCI could be present before patients received any cancer treatment. Olson and Marks (2019) stated that earlier studies reported pre-treatment CRCI in 11 to 33% of breast cancer patients, but more recent studies with a wider variety of cancer types have found rates as high as 46%. This pre-treatment CRCI is not to be taken lightly, as Baekelandt et al. (2016) reported that pre-treatment cognitive function was a significant predictor of survivability for pancreatic ductal adenocarcinoma, one of the deadliest forms of cancer. When comparing a group of low pre-treatment cognitive function patients to high pre-treatment cognitive function patients, Baekelandt et al. (2016) estimated that the hazard ratio of dying was 3.5 times more likely for the low function group (95% CI [1.7–7.3], *p* = 0.001).

While the mechanisms driving pre-treatment CRCI (and its potentially dangerous implications) are not fully determined, recent research has raised some considerations. Firstly, tumor cells have been known to induce an inflammatory response, which will be discussed in more detail later (Olson & Marks, 2019). In addition, tumors can create their own microenvironments, complete with their own macrophages, dendritic cells, and lymphocytes (Seruga et al., 2008). These tumor macrophages produce molecules that can pass through and alter junctions in the BBB (Nielsen & Schmid, 2017). This may start the chain leading to structural damage in the CNS, as Olson and Marks (2019) reported that pre-treatment cancer patients exhibited reduced cortical surface area or thickness in the temporal and frontal lobes, and lower white matter volumes in the frontal, parietal, and limbic regions. There is burgeoning evidence that this damage from cancer cells could be a driving factor in CRCI. Li et al. (2022) analyzed differences in cognitive impairment based on levels of Ki-67, a protein secreted by tumor cells that is used as a biomarker for tumor malignancy and proliferation. The authors reported that a higher level of Ki-67 was associated with worse cognitive function on the Mini-Mental State Examination (Li et al., 2022). As these results are only preliminary evidence, further research could establish if there is a threshold of malignancy where the development of a tumor begins to impact CRCI. With a wider array of cognitive assessments, researchers could also establish if there are certain cognitive domains associated with tumor-driven CRCI.

**The Role of Genetics**

It is possible that some people are more genetically predisposed to developing CRCI than others. One genetic variation that has received a lot of attention in research is the polymorphisms of apolipoprotein E (APOE). This protein plays a central role in lipid transport and uptake, providing the necessary nutrients for neural repair (Ahles & Saykin, 2007). This protein has been linked to CRCI, as Ahles & Saykin (2007) expressed that survivors carrying at least one E4 allele of APOE had lower scores of visual memory, spatial ability, and executive function than E3 allele carriers. Another polymorphism important for its role in neurogenesis is BDNF. Ren et al. (2019) reported that patients carrying the BDNF *Val* allele had worse performance on multitasking and verbal fluency assessments, while the BDNF *Met* allele seemed to play a protective role against CRCI development. These two types of genetic variations raise the possibility that genes relating to the ability of the CNS to heal itself can impact the severity of CRCI. In a different sector of CNS health, Li et al. (2022) found that different genotypes for catechol-O-methyltransferase (COMT), an enzyme that breaks down neurotransmitters, experienced different levels of cognitive function. In particular, the risk of developing CRCI was significantly lower in patients with the A/G genotype of COMT rs737865 than in patients who had the A/A genotype (Li et al., 2022). Thus, it is possible that through neurotransmitter regulation, enzyme polymorphisms may impact a patient’s susceptibility to CRCI.

**Patient Traits**

There are multiple characteristics about a patient or survivor that can contribute to their experience of CRCI, including age, race/ethnicity, and gender. Age has been one of the most established characteristics of a patient that contributes to CRCI. One reason for this association is the role of telomeres and neurodegeneration. Not only is telomere shortening a side effect of chemotherapy, but the progressive shortening of telomeres over time is considered one of the biological mechanisms of aging. The confounding effects of degeneration through age and cancer have been linked to memory and learning deficits (Cheung et al., 2013). In another avenue, Ahles et al. (2010) illustrated the connection between age, a lower pre-treatment cognitive reserve, and lower performance on a processing speed task. The authors raised the possibility that older patients may have less cognitive and neuronal resources, so the depletion of resources from cancer and its treatment could make CRCI more evident.

In their review on race, ethnicity, and CRCI, Franco-Rocha et al. (2023) reported that from the 25 articles they evaluated, 96% of the ethnic subgroup associations were significant. The authors stated that nine studies indicated a higher chance of Black or non-white patients reporting CRCI, while a tenth study reported that white patients were more likely to report more severe CRCI symptoms (Franco-Rocha et al., 2023). An additional study indicated that cognitive decline was slower for non-Hispanic Black patients (Franco-Rocha et al., 2023). Contributing to the problems of CRCI measurement, Franco-Rocha et al. (2023) reported that subjective CRCI measures, including FACT-Cog, are less effective at measuring CRCI in non-white populations. Altogether, this review illustrated that there is a racial and ethnic component to CRCI, so future research will be necessary in order to understand what drives the differences reported.

From the early stages of CRCI research, gender was proposed to play a role in dysfunction through hormones. Cheung et al. (2013) reported that estrogen and testosterone can both serve neuroprotective roles, acting as potential safeguards against telomere shortening. On the flip side, cancer initiates early menopause in women, resulting in a sudden drop in the levels of estrogen, and raising the risk of CRCI (Cheung et al., 2013). Additionally, differences in gender roles may influence CRCI. In a study on gender roles and CRCI, Jung and Cimprich (2014) found that a collectivist mindset and childbearing burden were both significant predictors of CRCI. The authors proposed that if a woman plays the primary role of family caretaker, they may experience more cognitive drain, leaving less reserve for their own cognitive performance (Jung & Cimprich, 2014). While few studies include estrogen levels or caretaker burden, there is building evidence that CRCI symptoms may be more severe in women. In a longitudinal study on young adult cancer patients, Tan et al. (2020) found that gender was associated with a higher likelihood of reporting CRCI on the FACT-Cog, β = -7.9, *p* = 0.02, 95% CI [-14.5, -1.3]. The impact of gender was especially noteworthy, as even chemotherapy and radiation were not significant predictors of CRCI (Tan et al., 2020). This gender difference in CRCI was even more drastic in a multisite study of 546 Hispanic adults performed by Parada et al. (2023). Patients completed an extensive series of neurocognitive tasks at their first appointment, then repeated the assessments at their 7-year follow-up appointment. Parada et al. (2023) reported that while female survivors experienced significant declines in memory (as well as near-significant decline in multiple other domains, such as episodic learning and verbal memory) male survivors actually had improved scores for language, verbal memory, executive function, and episodic learning. Could the diminished neuroprotection from cancer-initiated menopause result in sustained impairment for women? Are there gender differences in cognitive drain and CRCI recovery? As is the case with most CRCI research, there are a thousand possible routes that have yet to be pursued to understand these differences.

**Mental Health Factors**

Mental health factors such as stress, depression, and anxiety have all been connected to CRCI, leading researchers to question the often-circular nature of the relationship between psychological distress and CRCI. Quite understandably, being diagnosed with cancer and receiving treatment can be an extremely stressful experience. On the flip side, chronic stress has been linked with tumorigenesis, tumor malignancy, and cancer progression, creating a dangerous cycle between stress and cancer (Dai et al., 2020; Moreno-Smith et al., 2010). In addition to directly impacting cancer development (and the CRCI severity associated with the cancer itself) stress has been shown to exacerbate CRCI symptoms. For example, in a study on pre-treatment breast cancer patients, Aspelund et al. (2024) reported that stress significantly predicted CRCI (β = -0.52, *p* = 0.049). The role of stress in cancer outcomes received a critical measure of legitimacy with the release of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), as illnesses, such as cancer, were recognized as preceptors of posttraumatic stress disorder (PTSD; French-Rosas et al., 2011). With a clinical threshold for evaluating cancer-related stress, researchers could compare CRCI across sub-groups of cancer patients. Hermelink and colleagues (2015) utilized these standards to assess the impact of cancer-related PTSD on error scores from a series of computerized attention tasks (Tests of Attentional Performance, TAP) and found that PTSD symptoms significantly predicted error scores (β = 0.27, *p* = 0.004). In 2017, the authors completed a follow-up study that re-evaluated PTSD and CRCI after treatments were completed, and again a year after the patients’ first assessments. Interestingly, Hermelink et al. (2017) reported that in linear mixed-effect models, PTSD symptoms did significantly predict CRCI, but in exploratory nonparametric bivariate analyses, there were significant correlations between PTSD and attention errors at both Time 2 and Time 3. While the authors did not go into detail on their exploratory analyses, their results do raise interest in an important, but not linear, relationship between stress and CRCI.

Though they may not be as deeply intertwined with cancer as stress, both depression and anxiety can impact CRCI outcomes in unique ways. While there have been mixed results when using objective measures of CRCI, there are often strong, inverse relationships between depression and self-report CRCI assessments (Yang & Hendrix, 2018). The conflicting results in the associations with depression between subjective and objective measures of CRCI have raised a debate about the possible need for a mood correction factor within CRCI self-report assessments. Interestingly, anxiety has not seen as many inconsistencies in CRCI impact. Many studies find a strong correlation between the FACT-Cog and the Beck Anxiety Inventory. Cheung and colleagues (2012) even found this correlation to be significant (*r* = –0.58, *p* < 0.001) for a large sample of Asian breast cancer patients, despite concerns that these American-normed assessments may not be as accurate in other cultures. In opposition to depression, anxiety has more consistent relationships with objective measures of CRCI. For example, Chen et al. (2021) illustrated that anxiety could mediate the relationship between cancer status and a neuropsychological verbal fluency task (β = 0.80, t = 3.85, p < 0.001). As depression and anxiety are frequently conjoined (be it in comorbidity or research designs), the unique impacts they have on CRCI further illustrate the complexity of this dysfunction. When you combine all the possible variations in cancer treatments, cancer types, genetics, demographics, and mental health factors, the possible routes to a cause for CRCI become endless. It is this lengthy list of possibilities that drove researchers at the Banff Conference to discuss what underlying mechanism could connect all these contributing factors to CRCI (Tannock et al., 2004). By comparing CRCI to the animal model sickness behavior, researchers began to question if inflammation may be an important component of cancer cognition.

**The Potential Role of Inflammation**

The early 2000s saw an explosion of CRCI research illustrating that patients from a wide variety of cancers, treatment regimens, and demographics could all experience similar cognitive deficits and physical symptoms. Hierarchical cluster analysis of cancer side effects established that cancer symptoms often had clusters for appetite loss, pain, fatigue, and attention deficits, which were markedly similar to the symptoms of animal sickness behavior, such as wasting, pain, decreased social and habitat exploration, and impaired learning (Cleeland et al., 2003; Lee et al., 2004). This comparison of cancer side effects to animal sickness behavior was especially important because of the magnitude of studies that had induced sickness behavior (rather than just assessing correlations). Most commonly, these sickness behavior studies injected either bacteria or purified pro-inflammatory biomarkers into small animals and established that intracerebral, intravenous, and subcutaneous administration could all induce an inflammatory response and sickness behavior (Lee et al., 2004). Thus, the potential for a similar role of inflammation in human cancer symptoms became a major focus in CRCI research (Tannock et al., 2004). The pursuit to understand this role is not only beneficial for its general contribution to our knowledge, however, as there is a vast history of being able to treat inflammation. By understanding the role and nuances of inflammation, there is hope to discover an avenue for CRCI treatment, providing a huge change in the quality of life for cancer patients and survivors.

Inflammation is a complex process, requiring extensive communication between different types of cells. When neural tissue is damaged, a foreign pathogen is discovered, or excess molecules are detected, a specialized group of macrophages, called microglia, are activated (Shabab et al., 2017). These activated microglia swarm to the target site to attack ‘suspicious’ or dead tissue and cells, all while signaling for aid with the release of small proteins, such as cytokines and chemokines (Shabab et al., 2017). Other cells that function in the neuroimmune response, such as neutrophils, lymphocytes, and astrocytes, can then swarm to help, all while releasing cytokines and chemokines of their own (Nguyen & Ehrlich, 2020). In patients with cancer, tumor cells have been known to have their own microenvironment, including immune cells, that can also release cytokines (Olson & Marks, 2019). Though the flood of cells and nutrients through inflammation is a crucial part of healing, balance is pivotal, and it is important to avoid having too many immune ‘cooks in the kitchen.’ Measuring the levels of certain types of chemokines and cytokines can provide a biomarker for what types of messages are being shouted through the immune system, and in turn, determine if there is a healthy balance in the inflammatory response. While some of these signaling proteins are anti-inflammatory, such as interleukin (IL)-5, others are pro-inflammatory, such as interferon-alpha (IFN-α) and tumor necrosis factor-alpha (TNF-α; Seruga et al., 2008). Even more cytokines can function as both pro- and anti-inflammatory, including IL-2, IL-4, IL-6, and IL-10, though some may lean more towards one type of response than the other (Seruga et al., 2008). When the central nervous system is repeatedly flooded by too many pro-inflammatory protein signals, neuroinflammation can become chronic, with damaging side effects to the surrounding tissue (Nguyen & Ehlrich, 2020). Cytokines are one of the most common inflammation signaling proteins, and they can routinely be obtained from blood serum or cerebrospinal fluid, so they make a convenient measure to assess the state of neuroinflammation (Nguyen & Ehlrich, 2020). More importantly, as purified cytokines have been shown to induce sickness behavior in animals, there is a theoretical background to assessing cytokine levels in CRCI.

Our understanding of the relationship between cytokines and CRCI has grown substantially over the last 20 years. Interestingly, one of the earliest forays into assessing this relationship came before the field fully shifted toward the possibility that inflammation could play a role as a mediator. In 2001, Capuron and associates evaluated the impact of immunotherapies that included IL-2 and IFN-α cytokines on patients’ scores from three domains of the Cambridge Neuropsychological Test Automated Battery, but found slightly contradictory results. While patients who received IFN-α immunotherapy only had significantly lower scores on the multiple-choice task, the IL-2 immunotherapy group had significantly lower scores on the spatial working memory task and the spatial planning task (Capuron et al., 2001). Surprisingly, a subgroup of patients who received both IL-2 and IFN-α immunotherapy actually performed better on the spatial planning task, leading researchers to question how these cytokines were either promoted or counteracted by other cytokines. In hindsight, this article also laid the groundwork for illustrating that not all cytokines are cytotoxic and that there is a balance to be found between the neuroprotective and neurodegenerative components of inflammation. This balance was further highlighted in a paper often regarded as one of the first (well-known) studies to assess cytokine differences in CRCI. Meyers and associates (2005) reported that while higher levels of IL-6 were correlated with worse executive function on the Trail Making Test Part B, higher levels of IL-8 were correlated with better memory on the Hopkins Verbal Learning Test. In other words, the effects of an inflammatory response can differ based on the cytokines involved and the cognitive domain.

Importantly, this dual, neuroprotective/ neurodegenerative nature of inflammation is illustrated in both objective and subjective measures of CRCI, despite the difficulties with assessments. In a study evaluating blood serum concentrations of cytokines and performance on the Headminer™ neuropsychological test and the FACT-Cog, Cheung et al. (2015) reported that more severe subjective cognitive impairment was associated with higher concentrations of IL-6 (*B* = -0.92, *p* = 0.018) and interleukin-1 beta (IL-1β; *B* = -0.44, *p* = 0.001). On the neuroprotective side, every unit of IL-4 blood serum concentration was associated with a 0.95 increase in the FACT-Cog score (*p* = 0.022), indicating that IL-4 improved subjective CRCI (Cheung et al., 2015). It is worth noting, however, that while previous research raised the possibility that IL-8 could play a neuroprotective role, in this study, the relationship between FACT-Cog and IL-8 was not significant (Cheung et al., 2015). Though the relationships between cytokines and the memory and attention domains of the Headminer™ task were non-significant, Cheung et al. (2015) did state that each unit in IL-1β serum concentration was associated with a 0.78 decrease in response speed performance (*p* = 0.023), while each unit in IL-4 was associated with a 0.74 increase in response speed performance (*p* = 0.022). Not only do these results illustrate that we can capture specific differences in CRCI, but they also provide hope that a balance in inflammatory response could be a potential avenue for CRCI treatment. What the ideal, individual cytokine concentrations are to maintain this balance has yet to be determined. However, there is an undeniable impact on CRCI when the balance is disrupted and patients are faced with chronic neuroinflammation.

**The Damaging Effects of Inflammation**

The human body is largely composed of balancing systems within balancing systems, and the immune response is no exception. In a healthy body, cells perform actions that use energy, often in the form of electrons. When a cell completes a function, it uses an electron from a molecule and then releases the newly electron-deprived molecule, which is called a free radical, back into the system. Free radicals, such as molecules belonging to the reactive oxygen species (ROS), do not like being deprived of an electron, so will try to steal an electron from a different molecule. To prevent this chain of electron stealing, the body releases antioxidants, which scavenge excess ROS, keeping the body in balance. Oxidative stress occurs when ROS production expands past the capacity of antioxidants. This is important for inflammation, as free ROS activate microglia, triggering their functions as macrophages (an action that results in additional ROS byproduct) and their release of cytokines (McLeary et al., 2019). Tangpong et al. (2007) demonstrated that cytokines like TNF-α could also generate ROS, further perpetuating the inflammatory response. As the ratio of ROS to antioxidant molecules grows, the negative feedback loop of a healthy system is turned into a vicious spiral of chronic inflammation. This oxidative stress damages a cell’s mitochondria, causing mitochondrial dysfunction and apoptosis (Rummel et al., 2021). As this spiral of chronic inflammation and oxidative stress kills cells, fewer antioxidants are released, exacerbating the problem (Rummel et al., 2021). The damage from this process is severe enough that Wang et al. (2015) reported that oxidative stress is the leading cause of neuronal death. In cancer patients, this spiral is especially evident. Bagnall-Moreau et al. (2019) reported that cancer treatments like doxorubicin produce free radicals, triggering the oxidative stress spiral. The authors reported that this unchecked inflammatory response resulted in impairments in DNA translation and structural damage to the hippocampus (Bagnall-Moreau et al., 2019). As similar damage was reported when assessing the direct effects of cancer treatment on CRCI, what role does inflammation play in the damage inflicted by cancer treatment?

**Inflammation and Cancer Treatment**

As discussed previously, cancer treatment can impact CRCI bypassing the BBB and causing structural damage, impairing neurogenesis, and altering neuronal transmissions. One of the easiest places to assess how inflammation could be the vehicle driving cancer treatment impact is illustrated at the BBB. While only some chemotherapies can make it through the BBB, cytokines can pass through in a multitude of ways (Ren et al., 2017). As cytokines are such small molecules, they can passively diffuse through leaky regions of the BBB or actively enter at receptor locations through endocytosis (Ren et al., 2017). Most alarmingly, Rahman et al. (2018) illustrated that cytokines such as interferon-gamma (IFN- γ) and IL-17A could open junctions in the BBB, allowing larger molecules to enter the brain within 60 minutes of cytokine administration. With the alterations to BBB permeability, the influx of cytokines and chemotherapy can trigger microglial activation, oxidative stress, and inflammation throughout the brain, resulting in hippocampus volume loss (Ren et al., 2017; Ren et al., 2019). As the hippocampus is vital to learning and memory, the structural damage from the inflammatory response could be disastrous for CRCI.

There is a burgeoning body of evidence to suggest that the flood of cytokines into the CNS reduces cognitive function. In a 2013 study on breast cancer survivors, Kesler and colleagues reported that not only did patients who received chemotherapy have higher cytokine levels than controls, lower levels of IL-6 and higher levels of TNF-α were associated with lower left hippocampal volume. In fact, TNF-α, IL-6, and the interaction of these two cytokines accounted for 51.1% of the variance in left hippocampal volume (*p* = 0.02; Kesler et al., 2013). The authors connected this cytokine-driven damage to CRCI, as cytokine levels and left hippocampus volume explained 48.2% of the variance in total scores on the Hopkins Verbal Learning Test (*p* = 0.04). When considering that structural damage is just one way that cancer treatment has been linked to CRCI, explaining nearly half of the variance in CRCI outcomes is outstanding. However, as most current research focuses on linear relationships and associations, more mediation analyses will be necessary to determine if chemotherapy and cytokines are both impacting structural damage, and thus causing cognitive impairment, or if the relationship between structural damages from treatment and CRCI is mediated (or moderated) by inflammation.

Another potential route that inflammation could be driving treatment impact on CRCI is through the alterations in transmission. Cytokines have been shown to influence the synthesis and reuptake of neurotransmitters, such as serotonin, dopamine, and glutamate, hindering the ability of the CNS to pass information (Capuron & Miller, 2011). Lyman and associates (2014) proposed that the synaptic dysfunction from cytokines impairs impulse strength and long-term potentiation, resulting in memory deficits. Additionally, Gibson and Monje (2021) acknowledged that as cytokines play a role in dendritic pruning, a chronic inflammatory response could result in over-pruning and loss of branch complexity. To assess how these deleterious effects of cytokines may play a role in CRCI, Shi et al. (2019) administered rounds of chemotherapy to mice, collected blood serum cytokine levels, performed an MRI scan, assessed cognitive impairment in the Morris Water Maze Test, and dissected the brains of the mice. The authors found that chemotherapy increased levels of IL-6 and TNF-α, while reducing levels of IL-4 and IL-10, both in the blood serum and across the entire brain. Shi et al. (2019) reported that the increased levels of IL-6 and TNF-α correlated with worse cognitive performance and increased dendritic spine elimination. These results provide preliminary evidence that cytokines could be driving impairment by damaging neural pathways in animal models. But does the pattern hold for human CRCI? In a multi-site study of 717 current cancer patients, Oppegaard et al. (2021) performed pathway impact analyses to assess which signaling pathways were significantly perturbed between groups with low and high scores on the Attentional Function Index. The authors related that of the 12 signaling pathways that were significantly more perturbed in the low-attention group, five pathways were related to inflammation, including the TNF, IL-17, and cytokine-cytokine pathways (Oppegaard et al., 2021). While correlation may not be causation, these patterns warrant performing more mediation studies to assess if the dysfunction caused by cytokines is the underlying mechanism behind cancer treatment CRCI.

The relationships between cytokines, neurogenesis, and CRCI are still largely unknown. However, through the comparison of CRCI to sickness behavior, we can consider another avenue for inflammation to impact cancer cognition. Liu et al. (2019) demonstrated that not only did the administration of IL-1 induce sickness behavior in mice, but chronic IL-1 production in the hippocampus inhibited neurogenesis. These findings are consistent with earlier studies, where IL-6, IL-18, and TNF-α could trigger the cell death of neural progenitor cells before they could differentiate into neurons (Lyman et al., 2014). As Nguyen & Ehrlich (2020) established that reduced neurogenesis correlated with memory impairment, there is a need for research that encompasses changes in cytokine levels, neurogenesis, and the domains of CRCI within the same project.

**Inflammation and Cancer**

As research has illustrated that CRCI can occur without receiving treatment, could inflammation contribute to tumor-driven CRCI? In a longitudinal study on colorectal cancer patients, Vardy et al. (2015) reported that while there were significant differences in CRCI between cancer patients and healthy controls, there were no differences in composite cognition scores between the subgroups who were treated with chemotherapy and those who only required a surgery. Furthermore, cancer patients, regardless of treatment regimen, had significantly higher levels of cytokines than healthy controls (Vardy et al., 2015). However, when assessing the connection between cytokines and cognitive scores the authors also noted that while IL-2, IL-8, IL-10, and IL-12 were all associated with the Cambridge Neuropsychological Test Automated Battery processing speed scores, none of the associations were significant (Vardy et al., 2015). Due to the difficulties in capturing CRCI in assessments, this lack of significance is not specifically the lack of a connection, so the question about what factor is driving patient pre-treatment CRCI remains. On one side of the argument, Wardill et al. (2016) proposed that as tumor cells both trigger an immune response from the body and release their own inflammatory markers, the presence of tumors may induce CRCI through the oxidative damage associated with inflammation. Alternatively, Mounier et al. (2020) suggested that patients who are genetically pre-disposed for cancer development may also be at risk of cognitive decline. Future research in CRCI could include more pre-treatment analyses, measuring inflammation, cognitive impairment, suspect genes (such as the APOE and BDNF genes discussed previously), malignancy, tumor locations, and cancer type to uncover any potential patterns in CRCI. Realistically speaking, this area of CRCI research is still very exploratory, so study designs that cast a wide net to evaluate associations may be more beneficial than confirmatory approaches that restrict possibilities. As a wider array of biomarker analyses raises the associated cost, approaching this sector of CRCI research may be more easily achieved within a group of collaborators.

**Inflammation and Patient Traits**

As humans are inherently varied and random, looking for causal relationships between inflammation and patient traits must be approached and interpreted tentatively. It is important to note, however, that this does not indicate a lack of importance, as searching for patterns in inflammation, patient traits, and CRCI may distinguish vulnerable populations and drive interventions. Based on our current knowledge, one population that may be especially vulnerable is older cancer patients, as age is frequently correlated with both subjective and objective measures of CRCI (Janelsins et al., 2022). This trend is not trivial, as Országhová and colleagues (2021) reported that age is one of the most established risk factors for CRCI. It is possible that this increased risk is due to higher levels of pro-inflammatory cytokines, as low-grade inflammation is frequently connected to the aging process (Michaud et al., 2013). There is also an added risk of comorbidity, as both age and inflammation are linked to other neurodegenerative disorders, such as Alzheimer’s disease (Mayo et al., 2021). The possibility for inflammation to impact CRCI in older patients from a variety of avenues illustrates the need for more age-based CRCI research. There is a great potential for impacting the quality of life in cancer survivors if we can understand the mechanisms of inflammation and successfully counteract any imbalances.

While there is less theoretical rationale or evidence to believe that other patient traits, such as ethnicity or gender, would have vastly different levels of inflammatory markers, the potential for population differences should not be ignored. Firstly, this lack of previous evidence could be partially due to a severe underrepresentation of minorities in cancer and CRCI studies (Kronenfeld et al., 2021). Disregarding the possibility of a minority-related difference in inflammation and CRCI could further inflate healthcare disparities. Secondly, as inflammation may be serving as a mediator in CRCI, we need to consider what factors can impact inflammation, especially factors that may be different between populations. Thus, future research that includes assessments for diet, exercise, hormones, healthcare access, sleep quality, and cognitive reserve could help elucidate the role of inflammation, and how we can design interventions that are sensitive to the needs of populations most at risk.

**Inflammation and Mental Health Factors**

The relationships between mental health, inflammation, and CRCI may be less direct, but they do illustrate the importance of system balance. Research has shown that cytokines that pass through the BBB can activate the hypothalamus, increasing cortisol concentrations until receptors in the hypothalamic-pituitary-adrenal (HPA) axis become desensitized, altering the feedback loop central to stress response (Tausk, 2023). At the same time, cytokines can damage the glucocorticoid receptors, further raising cortisol concentrations (Capuron & Miller, 2011). When the over-production of cytokines in an inflammatory response chronically disrupts the balance of the HPA axis, the functioning of the prefrontal cortex and hippocampus can be diminished (Dai et al., 2020). Importantly, dysfunction of the HPA axis is connected to chronic stress, depression, and anxiety (Ménard et al., 2016; Tafet & Nemeroff, 2020). Additionally, depression is linked to imbalances in serotonin, one of the neurotransmitters that cytokines dysregulate (Das et al., 2020). However, while there are potential connections between cytokines and mental health, it is not clear how they interact to impact CRCI. It is possible that mental health symptoms and cytokines covary, rather than have a unidirectional relationship, as there is little basis to claim that one factor comes before the other. However, a potential covariance does not negate the value of an inflammatory approach to research, as an inflammation-based intervention could potentially reduce CRCI both directly and through a lessening of mental health symptoms.

**Assessing Cancer-Related Cognitive Impairment in the Future**

Though the field of CRCI has run—not walked—forward over the last two decades, the movement onward has not been bereft of stumbles. The lack of homogeneity has made the interpretation and applicability of results murky, further complicating a very nuanced topic. It is expected that there will be some heterogeneity, as CRCI can include dozens of types of cancer, hundreds of treatment combinations, and countless individuals with their own unique combinations of genetics and characteristics. Though a necessary part of performing research, study designs can also drastically vary, including their approaches to comparison groups, analyses, and length of assessment, leading to a stretched interpretation of CRCI. For example, while some projects began assessments at a cancer screening appointment, other studies evaluated survivors 10 years after treatment cessation, and all are thought to assess CRCI (Aspelund et al., 2024; Henneghan et al., 2018). In a final blow, what constitutes as CRCI is vague (there are no diagnostic criteria for it), leading to an astoundingly wide variety of assessments. For just a few examples, some projects asked a patient’s family member how often they had noticed the patient struggle with a specific task, other studies recorded the number of words a patient could recall after a delay, while another study pulled cognition-related items from a fatigue task (e.g., “At the moment I feel heavy-headed;” Durán-Gómez et al., 2022; Janelsins et al., 2012; Yang & Hendrix, 2018). But despite the wide variety of cognitive domains, analyses, and time points, each study is assumed to be analyzing CRCI, making the interpretations of CRCI relationships even more convoluted. In a nutshell, CRCI is usually a very subtle shift in ability that results in an incredibly extensive impact on a patient or survivor’s life. But to understand what is causing CRCI, we need to capture that subtle shift. When combining the innate heterogeneity of CRCI with the widely varying series of measurements, it can be difficult to *consistently* capture the subtle shift in cognition.

**The Measurement of CRCI**

In addition to the Banff Conference promoting the use of the FACT-Cog, the International Cognition and Cancer Task Force helped shape CRCI research by publishing a series of recommendations in 2011 (Wefel et al., 2011). For study design, the authors suggested multi-site, longitudinal studies that collect a pre-treatment baseline (Wefel et al., 2011). The authors stated that self-report assessments have not been extensively validated, so researchers should rely solely on objective assessments (Wefel et al., 2011). For the neuropsychological assessments, the authors promoted the use of the Hopkins Verbal Learning Test-Revised (HVLT-R) to assess learning and memory, the Controlled Oral Word Association (COWA) to evaluate speeded lexical fluency and executive function, and the Trail Making Test (TMT) to measure psychomotor speed and executive function (Wefel et al., 2011). Notably, Wefel et al. (2011) acknowledged that other assessments (such as the Brief Test of Attention and WAIS-III Letter Number Sequencing) had been discussed, but did not meet their requirements, leaving researchers to select their own measures for working memory and attention. For an analysis plan, Wefel et al. (2011) promoted the use of reliable change indices, regression-based approaches, and longitudinal modeling (such as linear mixed-effect models). Though there were certainly still researchers who elected not to follow the suggestions of the task force, a substantial portion of the field has utilized at least one of their recommendations. For a list of assessments that have been used in CRCI research, the cognitive domains they measure, and their use in the literature, please see Table 1 in the Supplemental Material.

While this list of measurements is quite expansive, covering a wide array of domains, not all the assessments have illustrated significant differences in cognitive impairment for cancer patients. Whether the lack of significant differences in some of these studies is because there is no impairment to be found or if it was not an assessment well-tailored to CRCI is difficult to say, as these assessments are rarely used multiple times. However, there are some assessments that have frequently been able to capture differences in cognition for cancer patients. Notable among that list is the FACT-Cog (especially the FACT-Cog version 3), the Hopkins Verbal Learning Test (HVLT; both the Revised and Delay versions), and the Trail Making Test (TMT; both parts A and B).

Interestingly, while the HVLT and TMT are objective assessments that frequently illustrate significant differences for CRCI, they both have a history of not correlating with FACT-Cog, the most common subjective measure (e.g., Gan et al., 2011; Henneghan et al., 2018). The frequent lack of connection of FACT-Cog to the objective, neuropsychological tasks led to Wefel et al. (2011) recommending against using subjective measures in CRCI. However, rather than just accepting that self-report measurements will never be perfect and discarding them, it is worthwhile to challenge our assumptions with questions. Is perceived CRCI truly representing the same phenomena as the attention or executive function deficits seen in the objective measures? Since Tannock et al. (2004) proposed that self-report CRCI should include a control for current mood, how much of perceived CRCI is reflecting whether the patient feels like their life has been altered through cognitive dysfunction? Self-report CRCI ratings often rise after cancer survivors return to normal school or work, even though there is little theoretical rationale or evidence to suggest that symptoms would only get worse after survivors are healthier (Von Ah et al., 2018). While a biological mechanism to explain cognitive symptoms worsening during recovery cannot be ruled out, there is also a possibility that patients are less aware of their impairment until they try to return to ‘normal’ tasks. If there is a component of self-report CRCI that reflects the perception of life shift, it is possible that responsibilities and cognitive demand could drive group differences, rather than the measurement reflecting differences in functional cognitive abilities. This is not to say that perceived CRCI is not an important component of CRCI, since perceived CRCI has been so frequently linked to patient and survivor quality of life. It is possible that perceived CRCI simply refers to a separate aspect of and set of symptoms than objective CRCI.

The difference between perceived CRCI and objective CRCI could also play a role in the differences seen in individuals who were higher performing before cancer development. At the Banff Conference, the concern was raised that in some of the studies with a non-significant difference between patients and healthy controls, a pattern from interviews indicated that these patients may have had above-average cognitive abilities before cancer development (Tannock et al., 2004). It is possible that the patients are more in tune with their own shift in abilities, leading to self-report analyses that saw group differences while objective assessments did not. With the small sample sizes of many early CRCI studies, these higher-performing individuals could be masking group differences. Moving forward, assessing individual differences across multiple time points can provide some clarification, but the inability to obtain a pre-cancer baseline will always leave researchers partially in the dark about the impact of pre-cancer cognition on a patient’s cancer experience. When considering the fact that there could be components of the cancer experience captured in subjective measures but not objective measures, it may be advisable to always include both forms of cognitive assessment, rather than throwing one out for being too different from the other.

**Analysis Plans for CRCI**

In keeping with the recommendations from the International Cognition and Cancer Task Force, a majority of studies over the last ten years have analyzed CRCI with simple linear regression, followed by linear mixed-effect model approaches. However, as we search for biological mechanisms that can explain CRCI, linear assumptions may actually be encumbering our ability to discern meaningful relationships. As discussed earlier, most biological factors are designed to maintain equilibrium, including pro- and anti-inflammatory responses. Disturbing the balance by having too much of a factor is just as damaging as having too little. This is counterintuitive to linear approaches, where continuing to go in one direction will always lead to improvements. In terms of an inflammatory response, assuming increases in pro-inflammatory cytokines will always worsen CRCI scores is completely ignoring that having too few pro-inflammatory cytokines can be just as detrimental. There must be some window in the middle where balance is maintained and cognition is optimized. Stepping beyond theoretical rationale, the possibility of equitable cytokine levels is beginning to emerge in research. In a novel approach, Henneghan and colleagues (2018) utilized random forest regression models to assess the connections between immune biomarkers and CRCI performance. After illustrating that the relationships were non-linear in bivariate analyses, Henneghan et al. (2018) fit models to each of the CRCI assessments. In one of these, the model for HVLT-delayed recall performance, the most important variables were IL-4, IL-1β, and TNF-α (RFR-adjusted *R2* = 0.75, *F* = 11.80, *p* = 7.34*-12*, Henneghan et al., 2018). Most fascinating of all, better HVLT-delayed scores were associated with TNF-α levels between 0.2 and 0.7 pg/ml (Henneghan et al., 2018). Not only does the inverted U created by this preliminary data illustrate that the relationship between CRCI and cytokines is not linear, it also provides hope that we can find an equitable level for each cytokine. Determining optimal levels for cytokines is no small undertaking, and it is quite likely that what is optimal for one person is different for another, or there may even be different optimal cytokine volumes for the separate domains of cognition. Future research that pursues the possibility of equitable cytokine levels would require copious amounts of work, but would have high potential for interventions.

As Henneghan et al. (2018) demonstrated the efficacy of non-linear models, CRCI research would highly benefit from building non-linear models to assess cytokines, CRCI, and the possible contributing factors listed earlier in this paper. Additionally, non-linear models could inform how we approach linear analyses. Consider the ideal TNF-α range in the HVLT task, for a simple example. If we can consistently reveal the same range for equitable TNF-α levels in non-linear analyses, we could use the peak or mean of our inverted U to determine the optimal level of TNF-α. By measuring the distance from the ideal to a patient’s actual volume of a cytokine, we could have another measure of immune imbalance to analyze. This measure of immune dysregulation—let’s call it imbalance bias—could even be used in linear approaches that a wider variety of researchers are familiar with. Rather than performing a linear mediation model to assess the impact of treatment on CRCI scores when mediated by cytokine volume averages, the researcher could look at how TNF-α imbalance bias mediates the effect of treatment on CRCI scores. Though it may not be a drastically different approach, it may reduce some of the error from using non-linear cytokines in a linear analysis. While this example is extremely over-simplified, and there are certainly more sophisticated analyses available, it does illustrate that when some researchers open their research plans to include non-linear approaches like random forest regression, more tools can be placed in the hands of all CRCI researchers.

A second approach to CRCI analyses that could be considered in future research is actually in the form of how we interpret the neuropsychological tasks. Many of these tasks (e.g., the Attention Network Test) measure a participant’s response time (Gaynor et al., 2022). From this distribution, researchers find the mean and standard deviation, which are then compared with other factors, such as chemotherapy. The potential problem with this approach is that response times are not normally distributed, so the mean and standard deviation may not be the best representatives of a patient’s impairment. Instead of assuming normalcy, researchers could fit the response time distributions with a different type of model, such as a shifted-Wald model or EZ-diffusion model (Anders et al., 2016; Wagenmakers et al., 2007). Fitting a patient’s Attention Network Test response time distribution with a shifted-Wald model would allow a researcher to decompose the model into three parameters: drift rate, shift, and response threshold. Drift rate refers to how a person accumulates information to drift towards a decision (like the decision to press a specific key on a keyboard) and often reflects the difficulty of a task. Shift refers to non-decision time, such as the time it takes to perceive letters on the computer during a task. Response threshold is the amount of information a participant needs before they can make a choice. Not only would utilizing a shifted-Wald model provide a much closer model fit, but the parameters could also be informative in analysis. For example, if a patient has relatively similar values for shift and response threshold at baseline, treatment midpoint, and end of treatment, but the drift rate continually got higher, the researcher could postulate that the participant did not experience any changes in the ability to perceive the information, but it was more difficult for them to drift to a decision. Additionally, the changes in these parameters could be compared across other factors, such as neurotransmitters or hippocampal volume. These expansions in analyses could be incredibly informative about the underlying mechanisms of CRCI.

**Biomarker Approaches**

Another sector of future research that could be remarkably informative is expanding the analysis of biomarkers. A main goal of CRCI research over the last twenty years was to establish if an inflammatory response could be connected to CRCI and the factors that contribute to CRCI. As discussed earlier in this paper, multiple studies have found these associations. Moving forward, rather than focusing on *if* there is a connection, research could focus on *how* this connection works. Is the inflammatory response an additional, independent factor that causes CRCI? Or is it the underlying mechanism that mediates the impairment from the other factors? Do all cytokines have the same impact, or do certain cytokines only cause dysfunction in specific cognitive domains? Preliminary data has illustrated some patterns, such as associations between IL-1B and slower performance speeds, IL-6 and worse executive function, and IL-8 and better memory performance, but these results have not been replicated consistently enough to determine if there is a basis for connecting certain cytokines to cognitive domains, or if they are spurious results that will fade in importance as the field grows (Országhová et al., 2021). If a true connection does exist, there may be a potential for administering specific cytokines or inhibitors as a targeted treatment for specific CRCI symptoms.

While cytokines have been the popular choice for biomarkers of inflammation, recent research has illustrated that there are many more biomarkers that should be assessed. As cancer treatments have been associated with structural damage, evaluating biomarkers for brain injury, such as amyloid beta (Aβ) and tau, could provide insight into how inflammation and structural deuteriation coincide (Didonna, 2020; Henneghan et al., 2020). In a similar approach to assessing the degenerative impact of treatment, Schroyen et al. (2021) provided preliminary evidence that the axonal damage marker, neurofilament light-chain (NfL), was associated with worsening CRCI scores, opening the possibility to assessing neuroplasticity and CRCI. Additionally, Leite et al. (2022) proposed that ouabain could provide information about the precursors to inflammation, as ouabain may be able to direct inflammatory responses, so incorporating this steroid into CRCI research may provide information about why specific areas of the brain receive more damage than others. The number of potential biomarkers has escalated quickly over the last five years, so expanding research beyond cytokines could allow researchers to assess the chain of effects that leads to CRCI.

**Inflammation-Informed Interventions**

As the role of inflammation in CRCI has become more evident, researchers have considered how an inflammation-informed intervention may provide a route for treating CRCI. As there is currently no treatment for CRCI, this possibility represents a massive beacon of hope. So far, there have been a few contenders. In their animal study, Keeney et al. (2018) found that the antioxidant 2-mercaptoethane sulfonate sodium (MESNA) could reduce oxidative stress and play a protective role against cognitive decline during doxorubicin administration. While it will be a substantial amount of time before an antioxidant intervention can be publicly implemented, this study provided preliminary evidence that reducing the inflammatory response could impact cognitive scores. Approaching inflammatory imbalance from a behavioral side, Pang and colleagues (2021) enrolled 128 breast cancer patients in an intervention, Cancer Managing and Living Meaningfully (CALM), designed to decrease anxiety and psychological distress. Remarkably, after enrollment in the intervention, the participants saw significant changes in both CRCI scores and cytokine levels (Pang et al., 2021). It is possible that even if CRCI has already begun, reducing the anxiety that can trigger an inflammatory response can stop the inflammatory spiral. As interventions can be implemented much faster than new drugs, the findings from this study provide a rationale for enrolling more patients in similar interventions, so cancer patients’ quality of life can be improved without needing to wait on drug trials.

While these inflammatory-informed interventions do present hope that we can improve the quality of life for cancer patients and survivors, it is necessary to note that a CRCI intervention based on the immune response would not be the perfect cure. For one reason, an anti-inflammatory approach may be counterproductive to treatments that utilize the body’s natural immune system to stop tumor growth. Additionally, there may be points within treatment, such as after surgery, where the medical professionals need to be alerted by the patient’s immune response, as it can be an indicator of a patient’s body rejecting an implant or sutures. With these potential constraints in mind, it is even more crucial to have a nuanced understanding of the immune role in CRCI, so interventions can be developed to help as many people as possible.

**Conclusion**

Twenty years ago, the field was just beginning to release how complicated CRCI can be. Since then, research has illustrated that cancer treatments, the cancer itself, genetics, and patient characteristics can all contribute to cognitive impairment for cancer patients and survivors. Through the similarities to the animal model of sickness behavior, researchers have been able to consider how an inflammatory response could mediate the effects on CRCI. When the immune response gets out of balance, the oxidative damage to a patient’s brain can be disastrous for cognitive abilities. While the deleterious role of inflammation is alarming, there is also an aspect of hope to be found if inflammation is driving CRCI. When CRCI was still considered ‘chemo-brain’ and the healthcare field assumed the impairment was only related to chemotherapy, there was less that could be done to treat CRCI. If the decision comes down to getting rid of cancer or having less cognitive impairment, most patients will choose to suffer the consequences of chemotherapy (though this is not the case for all patients). The chance of a CRCI treatment was negligible and distant. If inflammation is driving CRCI, though, interventions could be available relatively quickly, as there is a substantial understanding of anti-inflammatory medication. Thus, if future research can narrow in on the role of inflammation in CRCI, patients and survivors could see great improvements in quality of life. By utilizing a wide array of CRCI measurements and employing non-linear analyses of biological factors, the field could soon understand and treat cancer-related cognitive impairment.

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**Supplemental Material**

**Table 1**







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| CRCI Measure | Cognitive Domain | Source |
| Attention Network Test (ANT) | attention, executive function | Gaynor et al., 2022;  Jung & Cimprich, 2014 |
| Attentional Function Index (AFI) | attention | Oppegaard et al., 2021;  Yang & Hendrix, 2018 |
| Auditory Verbal Learning Test  (AVLT) | immediate and delayed memory | Yang & Hendrix, 2018 |
| Boston Naming Test | language | Gan et al., 2011 |
| Brief Visuospatial Memory  Test–Revised | memory encoding and retention | Gan et al., 2011 |
| Brief-Spanish English Verbal  Learning Test (B-SEVLT) | verbal learning | Parada et al., 2023 |
| Broadbent Cognitive Failures  Questionnaire | attention failures | Shilling et al., 2005 |
| California Verbal Learning Test | verbal memory | Ahles et al., 2010 |
| Cambridge Neuropsychological Test Automated Battery  (CANTAB) | motor skill, working memory,  spatial planning, rapid  processing | Capuron et al., 2001;  Janelsins et al., 2022;  Vardy et al., 2015 |
| Coding Task | psychomotor speed | Gaynor et al, 2022 |
| Color-Word-Interference Test | processing speed | Ahles et al., 2010 |
| Controlled Oral Word Association  Test (COWAT) | verbal fluency and word finding | Aspelund et al., 2024;  Henneghan et al., 2018;  Janelsins et al., 2022;  Jung & Cimprich, 2014;  Meyers et al., 2005 |
| Delis-Kaplan Executive Function  System Tests | processing speed, executive  functioning, language | Gan et al., 2011 |
| Digit Symbol Substitution Test | psychomotor speed | Parada et al., 2023 |
| European Organisation For Research And Treatment  Core Quality of Life Questionnaire (EORTC-QLQ) | quality of life | Baekelandt et al., 2015;  Cheung et al., 2012;  Heremelink et al., 2015 |
| Event-Based Prospective Memory  (EBPM) task | prospective memory | Li et al., 2022 |
| Fatigue Symptom Checklist Items | 5 items similar to cognition | Janelsin et al., 2012 |
| Finger Tapping | motor dexterity and speed | Gaynor et al, 2022 |

