What happens next? The Long-Term Impact of Cancer Treatment on Memory and Affective Symptoms in Breast Cancer Survivors

Meenakshie Bradley-Garcia

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School of Psychology
Faculty of Social Sciences
University of Ottawa

Supervisor: Dr. Melanie Sekeres

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ABSTRACT

Breast cancer is the most frequently diagnosed cancer worldwide, with increasing survival rates heightening awareness of long-term treatment-related effects on cognitive and mental health. Memory impairments are among the most commonly reported and functionally impactful complaints in survivors. However, most memory research relies on laboratory-based tasks that may not capture the complexity of everyday episodic memory, which depends on hippocampal mechanisms supporting the encoding and retrieval of rich contextual information and may be vulnerable to chemotherapy-related neurotoxicity. This thesis examines the long-term impact of breast cancer treatment on cognitive and psychological functioning across four objectives: (1) reviewing mechanisms underlying episodic memory impairment following cancer treatment, (2) characterizing long-term psychological outcomes and their interrelationships, (3) assessing episodic memory using standard and ecologically valid measures over short delays, and (4) evaluating memory for complex naturalistic events using film-based stimuli over extended delays, focusing on central and peripheral details.

We recruited Canadian women aged 30–65 years with a history of breast cancer who were at least six months post-treatment and age-matched non-cancer controls. During the first session, participants provided demographic and health information, and completed online questionnaires assessing stress, depression, anxiety, fatigue, and sleep quality. In the second session, participants completed two cognitive tasks to assess episodic memory using a narrative recall and verbal paired associates task, and two questionnaires to assess cognitive workload and perceived episodic and semantic memory abilities. In the final two sessions, participants viewed 40 short film clips and were asked to recall 20 clips immediately after encoding and the remaining 20 after a 7-day delay.

Breast cancer survivors reported higher levels of stress, depression, anxiety, fatigue, and sleep disturbance than controls, with each factor being interrelated. Breast cancer survivors recalled fewer verbatim and gist details for the narrative recall task than non-cancer controls, with impairments in gist memory persisting during delayed recall. However, no memory deficits were

evident on the paired associate task in breast cancer survivors. Breast cancer survivors reported greater cognitive effort during the story recall tasks, but no group differences emerged for the paired associate task. Survivors also reported greater cognitive effort during narrative tasks and greater subjective memory difficulties. In the film-based task, both groups showed comparable rates of forgetting over time; however, survivors recalled fewer central and peripheral details overall, with specific impairments for object-related and multimodal (spatial, auditory, and event-based) information.

The findings highlight the enduring cognitive and psychological sequelae of cancer treatment in breast cancer survivors, which may be partly influenced by the neurotoxic effects of chemotherapy on hippocampal functioning, a brain region critically involved in episodic memory. Although survivors performed similarly to non-cancer controls on standard neuropsychological memory measures, they demonstrated impairments on more complex, ecologically valid memory tasks, suggesting that traditional assessments may underestimate the everyday memory challenges experienced in survivorship. Furthermore, survivors exhibited difficulties recalling both gist-based and episodically rich details of naturalistic events, providing evidence of specific episodic memory vulnerabilities following treatment. Together, these findings support the need for comprehensive survivorship assessments incorporating ecologically valid cognitive measures alongside standard tests and subjective reports to better identify functional impairments and guide intervention strategies.

CHAPTER 1

Introduction

1. Breast Cancer

Among women, breast cancer is the most commonly diagnosed cancer worldwide, accounting for one in every four cancer diagnoses, and the leading cause of cancer-related death (Freihat et al., 2025; Sung et al., 2021). The course of treatment for breast cancer is determined by several factors, including the tumor size, location, stage, as well as the status of estrogen and progesterone hormone receptors (Akram et al., 2017). Standard treatment options include surgery, radiation therapy, chemotherapy, and hormonal therapy (Akram et al., 2017). Although advances in breast cancer detection and treatment have substantially improved survival rates (Héry et al., 2008; Wefel et al., 2015), growing evidence suggests that these treatments may have unintended consequences (Wefel et al., 2015). In particular, there is increasing recognition that cancer treatment can impact cognitive, psychological, and physiological functioning, as well as neural integrity, resulting in functional impairments.

2. Sequalae of Cancer Treatment

2.1 Psychological and physiological outcomes

Breast cancer survivors experience multiple stressors across the cancer trajectory, including diagnostic uncertainty, confirmation of malignancy, adjustment to illness, and the physical and functional consequences of treatment such as surgery and chemotherapy, which can disrupt social, occupational, financial, and personal functioning (Brandão et al., 2017; Hessami et al., 2025). Many also report fear of recurrence following remission, which may further contribute to elevated stress (Dunn et al., 2015).

Stress, anxiety, and depression vary across the disease course, with stress typically peaking following surgery and prior to chemotherapy (Aboalela et al., 2015; Alagizy et al., 2020), anxiety

highest at diagnosis and during treatment (Lopes et al., 2022), and depression most pronounced following diagnosis and prior to treatment (Alagizy et al., 2020; Donovan et al., 2004). Although symptoms generally decline after treatment, stress (Mazor et al., 2019), anxiety (Breidenbach et al., 2022; Browall et al., 2008; Lopes et al., 2022), and depression (Donovan et al., 2004; Lopes et al., 2022) may persist for up to five, six, and one years post-treatment, respectively.

In addition to psychological distress, breast cancer survivors also experience enduring physiological changes, including sleep disturbances and fatigue, due to cancer treatment. Sleep disturbances affect between 20% and 70% of individuals following treatment (Alfano et al., 2011; Fiorentino & Ancoli-Israel, 2006). These disturbances include reduced restorative sleep and difficulties initiating and maintaining sleep, and they may persist for up to a decade after treatment (Alfano et al., 2011; Fiorentino et al., 2011; Fiorentino & Ancoli-Israel, 2006; Momayyezi et al., 2021; Palesh et al., 2007; Sanford et al., 2013; Trudel-Fitzgerald et al., 2017). Fatigue affects approximately 60% to 90% of women during treatment, particularly among those receiving chemotherapy (Andrykowski et al., 2005; Banipal et al., 2017; Donovan et al., 2004). Similar to psychological impacts, physiological symptoms often emerge before treatment begins, intensify throughout treatment, and although they gradually decline over time (Andrykowski et al., 2005; Biering et al., 2020; Bower et al., 2000; Ganz & Bower, 2007).

These symptoms rarely occur in isolation and often reinforce one another. Rather, stress, depression, anxiety, sleep disturbance, and fatigue frequently co-occur and interact, contributing to a cumulative symptom burden (Aggeli et al., 2021; Fardell et al., 2023; Levkovich et al., 2015; Momayyezi et al., 2021; Wang et al., 2020; Williams et al., 2021).

2.2 Cognitive outcomes

Cancer and its treatments are also associated with changes in cognitive functioning. Breast cancer patients and survivors commonly report difficulties with attention, memory, problem-solving, and processing speed (Horowitz et al., 2019; Janelsins et al., 2011; Joly et al., 2015). Although

cognitive impairments are reported by up to 75% of breast cancer survivors during treatment, these difficulties do not always resolve following treatment completion (Janelsins et al., 2011; Lange et al., 2019; Wefel et al., 2004). Approximately 35% of survivors continue to experience cognitive symptoms long-term (Janelsins et al., 2011), with some studies documenting impairments up to 20 years after chemotherapy treatment (Amidi et al., 2015; Koppelmans et al., 2012; Schagen et al., 1999). These cognitive changes are assessed using both objective and self-reported measures (Hutchinson et al., 2012; Janelsins et al., 2017; Oliva et al., 2024). Notably, discrepancies between these approaches are common, as breast cancer survivors often report cognitive decline following chemotherapy despite minimal or absent deficits on objective neuropsychological tests (Hutchinson et al., 2012; Janelsins et al., 2017; Oliva et al., 2024).

2.3 Functional outcomes

These cognitive, psychological, and physiological difficulties can interfere with a range of everyday activities, including managing daily responsibilities and maintaining independence (Boykoff et al., 2009; Von Ah et al., 2013). Such challenges may also hinder survivors' ability to return to work (Munir et al., 2010; Von Ah et al., 2013), self-confidence (Von Ah et al., 2013), and social relationships (Boykoff et al., 2009; Von Ah et al., 2013). Together, these functional, occupational, and psychosocial difficulties can persist long after treatment completion and contribute to significant reductions in the quality of life of breast cancer survivors (Boykoff et al., 2009; Tannock et al., 2004).

3. Memory

Among the cognitive changes reported following cancer treatment, memory difficulties are among the most common and distressing cognitive concerns expressed by breast cancer survivors (Amani et al., 2024; Ganz et al., 2013; Rodrigues et al., 2023). Consequently, understanding the nature of memory and the neural systems that support it is critical for characterizing memory impairments following cancer treatment.

3.1 Declarative Memory

Memory is commonly divided into short-term and long-term systems (Atkinson & Shiffrin, 1968). Short-term memory has a limited capacity and retains information for the duration of seconds (Cowan, 2008; Miller, 1956). In contrast, long-term memory supports the storage of large amounts of information over extended periods, ranging from minutes to years (Cowan, 2008). Long-term memory can be further categorized into implicit and explicit memory systems (Squire, 2004; Squire & Zola, 1996). Implicit (non-declarative) memory supports learning that occurs without conscious awareness, including procedural skills, classical conditioning, non-associative learning, and priming (Dickerson & Eichenbaum, 2010; Squire, 2004; Squire & Zola, 1996), whereas explicit (declarative) memory relates to conscious recollection of facts and events (Squire, 2004; Squire & Zola, 1996).

Declarative memory comprises two interrelated but functionally distinct components: semantic and episodic memory (Dickerson & Eichenbaum, 2010; Renoult et al., 2019; Tulving, 1972). Semantic memory refers to general knowledge about the world, including facts, concepts, and meanings (Dickerson & Eichenbaum, 2010; Renoult et al., 2019; Tulving, 1972). Episodic memory, in contrast, enables the recollection of personally experienced events and includes information about the "what, where, when" of the episode (Dickerson & Eichenbaum, 2010; Renoult et al., 2019; Tulving, 1972). For instance, when considering a seagull, semantic memory would include general knowledge about the animal, such that it is a bird that has grey and white feathers with long wings. By comparison, an episodic memory might involve recalling a specific personal experience, such as a seagull stealing one's lunch on a Saturday afternoon in August 2020 in downtown Ottawa.

Naturalistic episodic memories can be characterized by both central and peripheral details of an event (Sekeres et al., 2016; Sekeres, Winocur, Moscovitch, et al., 2018). Central details represent information essential to an event's narrative structure, whereas peripheral details comprise descriptive, perceptual, and contextual features that enrich the memory but are not necessary for understanding the core event (Sekeres et al., 2016; Sekeres, Winocur, & Moscovitch, 2018). Using

the previous example, central details would include the general schematic representation of the event (e.g., the theft of someone's lunch by a seagull), whereas peripheral details would reflect the episodically rich details of the event (e.g., bird's appearance, the individual's clothing and location, the weather and time of year, the surrounding urban environment, background activity, and ambient sounds). Although memory for both central and peripheral details decline over time, peripheral details are particularly susceptible to forgetting (Sacripante et al., 2022; Sekeres et al., 2016; Sekeres, Winocur, & Moscovitch, 2018). Consistent with this, individuals with medial temporal lobe damage show disproportionate impairments in recalling peripheral elements of episodic memories, while central details remain relatively persevered (Gilboa et al., 2006; Rosenbaum et al., 2005; Steinvorth et al., 2005; St-Laurent et al., 2009). Measures including both central and peripheral details provide a sensitive means of detecting subtle memory impairments associated with hippocampal dysfunction (Hayes et al., 2004; St-Laurent et al., 2014, 2016).

3.2 Neurobiology of Episodic Memory

Episodic memory relies on a distributed network of brain regions that support encoding, consolidation, and retrieval of long-term memories (Squire, 2009). Central to this system is the medial temporal lobe (MTL), comprising the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex (Dickerson & Eichenbaum, 2010). Within this system, the hippocampus plays a particularly critical role, supporting the formation and retrieval of episodic memories by integrating information across these interconnected regions.

Although episodic memories may initially be encoded as richly detailed representations, they are not static and undergo transformation over time. According to the Trace Transformation Theory, memories are initially highly dependent on the hippocampus and are rich in episodic details (Gilboa & Moscovitch, 2021; Sekeres et al., 2024; Sekeres, Winocur, & Moscovitch, 2018). As this transformation occurs, retrieval becomes progressively less dependent on the hippocampus and increasingly reliant on distributed neocortical systems, such as the medial prefrontal cortex (mPFC),

which is thought to support schematic and generalized memory representations (Gilboa & Moscovitch, 2021; Sekeres et al., 2024; Sekeres, Winocur, & Moscovitch, 2018; Tarder-Stoll et al., 2025). Within this framework, both hippocampal-dependent episodic traces and neocortical schematic representations can coexist in memory over time (Gilboa & Moscovitch, 2021). This transformation framework further highlights that when hippocampal integrity is compromised, the encoding and retrieval of detailed episodic traces is disproportionately affected, resulting in a reliance on schematic representations and a reduction in access to richly detailed content (Gilboa et al., 2006; Rosenbaum et al., 2005; St-Laurent et al., 2009).

While the hippocampus is critical for episodic memory, its function depends on interactions with a broader large-scale brain network that substantially overlaps with the default mode network (DMN). Key regions within this network include the medial prefrontal cortex, posterior cingulate cortex, and lateral parietal cortex (Raichle, 2015). The DMN is associated with internally oriented cognition, including self-referential thought, emotional processing, mind-wandering, and the retrieval of episodic memories (Azarias et al., 2025; Huijbers et al., 2011; Jeong et al., 2015). Functional connectivity between the hippocampus and DMN regions has been linked to successful memory retrieval, suggesting that episodic remembering depends on coordinated activity across both medial temporal and cortical memory systems (Mccormick et al., 2013).

3.3 Neurobiological Alterations in Breast Cancer Patients

Neurobiological evidence suggests a potential mechanism contributing to memory impairments in breast cancer survivors. While chemotherapy remains central to cancer treatment, its neurotoxic effects, dependent on factors such as drug type, dosage, and administration frequency, pose serious risks to cognitive health (Sekeres et al., 2021). Notably, several chemotherapeutic agents used in the treatment of non-central nervous system cancers, including breast cancer, are capable of crossing the blood–brain barrier, where they may exert neurotoxic effects on brain regions critical for episodic memory, particularly within the MTL, including the hippocampus (Alhowail, 2025; Bagnall-

Moreau et al., 2019; Sekeres et al., 2021; Wardill et al., 2016; Winocur et al., 2018; Yang & Moon, 2015). Preclinical and clinical studies have identified a range of chemotherapy-related structural alterations, including reduced hippocampal volume, hippocampal deformation, impaired neurogenesis, increased neuroinflammation, and disruptions in both grey and white matter integrity (Apple et al., 2017; Bergouignan et al., 2011; Daniel et al., 2024; Dietrich et al., 2008, 2015; Murillo et al., 2023). Functional neuroimaging studies have further revealed altered patterns of neural activity, including prefrontal hyperactivation and disruptions within the default mode network (Chen et al., 2021; Dietrich et al., 2015; Feng et al., 2020; McDonald et al., 2012). These alterations may also help explain the common discrepancies between objective cognitive performance and subjective cognitive complaints, which is thought to reflect increased reliance on effortful, compensatory neural processes to maintain task performance at levels comparable to controls (Ansari & Derakshan, 2011; Berggren & Derakshan, 2013).

Together, these findings suggest that cancer treatment may compromise neural systems supporting episodic memory while simultaneously increasing reliance on compensatory cognitive processes. Such compensatory recruitment may help explain the frequently observed dissociation between subjective cognitive complaints and objective cognitive performance, whereby survivors report substantial cognitive difficulties despite demonstrating relatively preserved performance on standard neuropsychological measures.

4. Objectives

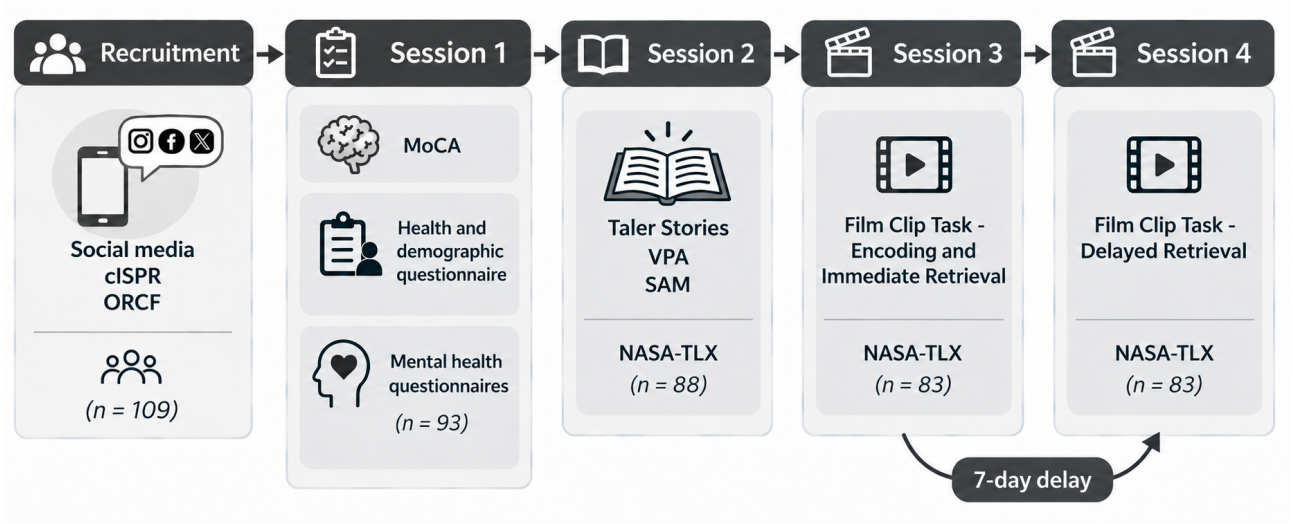
Although it is well documented that breast cancer survivors experience memory difficulties (Gaynor et al., 2022; Koppelmans et al., 2012; Quesnel et al., 2009; Root et al., 2016; Shibayama et al., 2014; Wirkner et al., 2017), alongside heightened stress (Aboalela et al., 2015; Alagizy et al., 2020; Mazor et al., 2019), anxiety (Breidenbach et al., 2022; Browall et al., 2008; Lopes et al., 2022), depression (Alagizy et al., 2020; Donovan et al., 2004; Lopes et al., 2022), sleep disturbances (Alfano et al., 2011; Fiorentino et al., 2011; Fiorentino & Ancoli-Israel, 2006; Momayyezi et al., 2021;

Palesh et al., 2007; Sanford et al., 2013; Trudel-Fitzgerald et al., 2017), and fatigue (Andrykowski et al., 2005; Biering et al., 2020; Bower et al., 2000; Ganz & Bower, 2007) during and following cancer treatment, the mechanisms underlying episodic memory changes remain poorly understood (Bradley-Garcia et al., 2022). A key limitation of the existing literature with breast cancer survivors is that episodic memory is typically assessed using decontextualized laboratory tasks such as word lists and paired-associate learning paradigms (Koppelmans et al., 2012; Quesnel et al., 2009; Root et al., 2016). While these measures are psychometrically robust and experimentally well controlled, they do not capture the contextual richness, temporal structure, or perceptual complexity of real-world memory experiences (Davachi & Dobbins, 2008; Lee et al., 2020). Moreover, because they were primarily developed to detect substantial cognitive deficits in clinical populations, they may lack the sensitivity needed to identify the subtle memory impairments often reported by breast cancer survivors (Ahles & Root, 2018). Similarly, although a range of psychological outcomes has been studied in breast cancer survivors, few studies have systematically examined multiple interrelated constructs within a unified framework. In addition, much of the breast cancer literature relies on pre–post treatment comparisons or comparisons between treatment groups, often without including a healthy control group. Although this approach can identify treatment-related changes, it limits the ability to determine whether observed outcomes differ from normative levels of cognitive and psychological functioning. This issue is particularly evident in mental health research (Aboalela et al., 2015; Alagizy et al., 2020; Golden-Kreutz et al., 2004; Jones et al., 2015), with fewer few studies directly comparing breast cancer survivors with non-cancer controls (Ando-Tanabe et al., 2014; Koppelmans et al., 2012; Lange et al., 2023).

To address these gaps, a comprehensive literature review was conducted to examine the neurotoxic effects of cancer treatment and their potential impact on episodic memory in breast cancer survivors (Aim 1). This review informed a cross-sectional study comprising four sessions with the same participants participating in each session (see Chapters 3–5 for recruitment details). In Session 1, participants completed demographic, health, and mental health questionnaires (Aim 2; see

Chapter 3 for more information). In Session 2, they completed a neurocognitive battery that included an ecologically valid memory measure, a standard laboratory task, and measures of cognitive workload and subjective memory functioning (Aim 3; see Chapter 4 for more information). In Session 3, participants viewed a series of short film clips and recalled half of them. During the fourth and final session, conducted after a seven-day delay, they recalled the remaining clips (Aim 4; see Chapter 5 for more information). See Figure 1 for a schematic representation of aims 2 to 4.

Figure 1. *Schematic representation of the study design for aims 2 to 4.* Abbreviations: cISPR, Integrated System of Participation in Research – Community Pool; ORCF, Ottawa Regional Cancer Foundation; MoCA, Montreal Cognitive Assessment; VPA, Verbal Paired Associates; SAM, Survey of Autobiographical Memory; NASA-TLX, NASA Task Load Index.



Aim 1: **A neurobiological framework for understanding episodic memory impairment (Chapter 2).** This chapter establishes a theoretical and neurobiological framework for understanding episodic memory dysfunction in breast cancer survivors. Specifically, it reviews evidence for potential neural mechanisms underlying memory impairments, with particular emphasis on structural and functional neuroimaging findings indicating alterations in the hippocampus and related medial temporal lobe regions.

Aim 2: **Long-term mental health outcomes (Chapter 3).** This chapter examines the long-term effects of cancer treatment on mental health outcomes in breast cancer survivors. It is hypothesized that, compared to non-cancer controls, breast cancer survivors will report significantly higher levels of stress, anxiety, depression, fatigue, and sleep disturbances. It is further expected that these variables will be positively intercorrelated.

Aim 3: Comparing standard and ecologically valid measures for detecting subtle episodic memory impairments (Chapter 4). This chapter investigates whether ecologically valid memory measures capture episodic memory deficits in breast cancer survivors that may not be fully detected using standard laboratory-based tasks. It is hypothesized that, relative to non-cancer controls, breast cancer survivors are expected to recall fewer details on a narrative story task, perform more poorly on verbal paired associates learning, and show greater impairment on the ecologically valid narrative task relative to the standard paired associates task. In addition, breast cancer survivors are expected to report greater cognitive effort during task completion and greater subjective complaints regarding both episodic and semantic memory in daily life compared to non-cancer controls.

Aim 4: Differential vulnerability of central and peripheral details in naturalistic event memory (Chapter 5). This chapter examines whether cancer treatment differentially affects encoding and retrieval of central versus peripheral details in complex event memory. It is hypothesized that, compared to non-cancer controls, breast cancer survivors will recall fewer central and peripheral details overall, with disproportionately greater impairments in peripheral detail recall. It is further expected that breast cancer survivors will show greater forgetting across time and increased difficulty recalling specific subtypes of peripheral details. Finally, breast cancer survivors are expected to report greater perceived cognitive effort during the completion of this memory tasks compared to non-cancer controls.

CHAPTER 2

Episodic Memory and Recollection Network Disruptions Following Chemotherapy Treatment in Breast Cancer Survivors: A Review of Neuroimaging Findings

Meenakshie Bradley-Garcia[1], Gordon Winocur[2,3,4] and Melanie J. Sekeres[1]

[1]School of Psychology, University of Ottawa, Ottawa, Ontario, Canada
[2]Rotman Research Institute, Baycrest Centre, Toronto, Ontario, Canada
[3] Department of Psychology, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[4]Department of Psychology, Trent University, Peterborough, Ontario, Canada

Authors note

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Abstract

Long-term memory disturbances are amongst the most common and disruptive cognitive symptoms experienced by breast cancer survivors following chemotherapy. To date, most clinical assessments of long-term memory dysfunction in breast cancer survivors have utilized basic verbal and visual memory tasks that do not capture the complexities of everyday event memories. Complex event memories, including episodic memory and autobiographical memory, critically rely on hippocampal processing for encoding and retrieval. Systemic chemotherapy treatments used in breast cancer commonly cause neurotoxicity within the hippocampus, thereby creating a vulnerability to memory impairment. We review structural and functional neuroimaging studies that have identified disruptions in the recollection network and related episodic memory impairments in chemotherapy treated breast cancer survivors, and argue for the need to better characterize hippocampally mediated memory dysfunction following chemotherapy treatments. Given the importance of autobiographical memory for a person's sense of identity, ability to plan for the future, and general functioning, underappreciation of how this type of memory is impacted by cancer treatment can lead to overlooking or minimizing the negative experiences of breast cancer survivors, and neglecting a cognitive domain that may benefit from intervention strategies.

Keywords: cognitive impairment; memory loss; breast cancer; chemotherapy; neuroimaging; medial temporal lobe; hippocampus

1. Introduction

Advances in diagnostic and therapeutic interventions for breast cancer have led to high patient survival rates [1]. The return to normal daily activities following cancer treatment is often hampered by treatment-related side effects that impact cognitive function [1,2]. In the months and years following treatment, up to 75% of women successfully treated with chemotherapeutic agents for breast cancer experience chemotherapy-related cognitive impairment (CRCI), or 'chemobrain', described by patients as a feeling of fuzzy headedness or mental slowness [3–5]. The most commonly observed symptoms, as assessed through neurocognitive testing, are long-term memory loss, attentional difficulties, and impaired executive functioning that affects planning, problem solving, and working memory [1,4,6–9]. These cognitive changes severely disrupt survivors' ability to carry out normal daily activities [4,7,10–12], and have a significant impact on overall quality of life. CRCI has been observed up to 20 years following treatment [3,13–15], with structural and functional differences evident in the brain for at least 10 years post-treatment [16–19]. These findings highlight the long-lasting and pervasive impact on the neural physiology and well-being of survivors [3].

CRCI has been seen in many other types of non-CNS cancers [20] but is most prevalent and most studied in breast cancer. Long-term memory disturbances are amongst the most common and disruptive symptoms experienced by breast cancer survivors following chemotherapy, yet the physiological mechanisms underlying disrupted memory processing following chemotherapy are not well characterized [21]. This narrative review and commentary focuses specifically on chemotherapy-related memory impairments in breast cancer survivors, including the largely neglected domain of autobiographical memory. We discuss potential neural mechanisms contributing to memory processing deficits, with a focus on structural (MRI) and functional (fMRI) neuroimaging studies identifying alterations in the hippocampus and related medial-temporal lobe structures in breast cancer survivors.

We searched the PubMed and Google Scholar data bases between 2000 and 2022 using the search terms 'chemotherapy', 'breast cancer', 'chemofog', 'chemotherapy-induced cognitive

impairment', 'episodic memory' 'long-term memory', 'autobiographical memory', 'resting state', 'default mode network', 'hippocampus', 'temporal lobe', 'MRI,' 'fMRI'. Papers were excluded if they did not include measures of long-term memory (delayed verbal memory, delayed visual memory, episodic memory, autobiographical memory) or structural or functional assessments of the temporal lobes or recollection/default mode network in chemotherapy-treated breast cancer survivors.

2. Physiological Mechanisms Contributing to Chemotherapy-Related Memory Disruption

The hippocampus, a medial-temporal lobe structure that is critical for memory processing, has been found to be particularly sensitive to structural and functional disruption following chemotherapy treatment [22]. The physiological mechanisms mediating these disruptions and related cognitive impairments are multifactorial, including breakdown of the blood–brain barrier, pro-inflammatory cytokine release (IL-6, IL-1B, TNF-α) [23], increases in reactive oxidative stress and mitochondrial dysfunction [24,25], enhanced activated microglia [26,27], neuronal morphology abnormalities including reduced dendritic branching and spine density in the hippocampus [27–29], and white matter microstructural changes, and reduced gray matter volume throughout the brain [30,31]. While these factors likely combine to exacerbate the broader cognitive dysfunction characterizing CRCI, a likely candidate mediating long-term memory loss following chemotherapy is a reduction in adult hippocampal neurogenesis.

Hippocampal subregions (CA1, CA3, and dentate gyrus) have specialized functions, with the dentate gyrus being of particular interest in understanding chemotherapy-related cognitive impairment and neurotoxicity due to its role in neurogenesis. The dentate gyrus is unique, in that it is one of two known regions to continually generate new neurons in the mammalian brain [32]. This process of hippocampal neurogenesis contributes to a renewing pool of neurons that functionally incorporate into new memory networks [33], and critically contribute to the process of memory consolidation [34], memory clearance [35,36], and cognitive flexibility [37]. Experimentally induced suppression of adult neurogenesis typically results in deficits on hippocampally mediated memory tasks in animal models [38–41].

Several molecular mechanisms referred to above have been linked to reduced rates of hippocampal neurogenesis. For example, cell damage induced by chemotherapy-induced increases in reactive oxidative stress reduces the survival of primary neural precursor cells and inhibits the production of new cells in the hippocampus [24,25,42,43]. Similarly, stress-induced expression of pro-inflammatory cytokines IL-6 and TNF-α suppresses doublecortin levels within the hippocampus, a cellular marker expressed by immature neurons [44].

The range of systemic chemotherapeutic agents commonly used in breast cancer therapy have been shown to suppress hippocampal neurogenesis and to impair hippocampally mediated memory in rodents, including the anti-metabolites methotrexate [45–48], 5-FU [49–52], cisplatin [53–55], alkylating agents cyclophosphamide [8,26,56,57], temozolomide [58–61], mitotic inhibitors doxorubicin [8,26,62] and paxlitaxel [50,63–65], both when used alone or in combination [29,39,66–72] (see Sekeres et al. [72] for extensive review of the classes of chemotherapy drugs and their effects on hippocampal neurogenesis and memory performance in pre-clinical models). These findings provide strong evidence that the neurotoxic effects of common breast cancer treatments are sufficient to induce cell-specific hippocampal neurotoxicity that, in part, mediates long-term memory deficits observed in patients.

In vivo structural neuroimaging studies in humans lack the spatial resolution to assess differences in dentate gyrus volume at the cellular level, and cannot distinguish natally generated neurons from adult-generated neurons. However, hippocampal segmentation analyses have identified differences in hippocampal sub-region volume between chemotherapy-treated breast cancer survivors and healthy controls, suggesting that systemic chemotherapy treatments are capable of inducing changes in the human hippocampal architecture [73]. Post-mortem observations in human brain tissue have confirmed that common cancer treatments (systemic chemotherapy, cranial radiation,) are capable of suppressing hippocampal neurogenesis [74].

Given the role of the hippocampus in memory processing, understanding changes in hippocampal integrity following various chemotherapy treatments is essential to understanding the

associated memory impairments in breast cancer survivors. Quantifying adult hippocampal neurogenesis remains a challenge in humans [75,76]. There is post-mortem evidence that adult hippocampal neurogenesis persists throughout the lifespan in humans, though some age-related declines in neurogenic rates are evident, particularly within the anterior hippocampus [77–79]. Treatments that impair the normal proliferation and survival rates of adult generated hippocampal neurons reduce the pool of new neurons available to support new memory encoding, and likely, in part, account for post-treatment memory disruptions experienced by cancer survivors [80,81].

3. Current Methods for Assessing Chemotherapy-Related Memory Disruption

Much of what is known about CRCI and its underlying cellular and molecular mechanisms has been identified in pre-clinical studies of rodents [22,31,72,82]. Pre-clinical models are critical for identifying physiological changes in response to various chemotherapy drugs with a high degree of cellular specificity [70,72], and have the advantage of controlling for confounding factors in human studies into the effects of chemotherapy drugs on neurocognitive function. These confounding factors include variations in drug types, dosage and treatment schedules, duration since treatment, methods of cognitive evaluation, as well as comorbidities and other forms of treatment. A major limitation to pre-clinical studies of cognition and behaviour as a model for CRCI, however, is that they fail to capture the nuanced cognitive disturbances experienced by cancer survivors. For example, while breast cancer survivors experiencing CRCI exhibit memory difficulties in various forms, standard tasks used to assess long-term memory in pre-clinical models are unidimensional (e.g., delayed place and object recognition tasks), and do not capture the complexities of human long-term memory processing.

This limitation in test complexity is not unique to pre-clinical measures. The most common neurocognitive tests of long-term memory performance in breast cancer survivors measure verbal and visual memory using standardized list learning, word or object recognition, or free recall tasks following a delay. These are well established tasks that are sensitive to mild cognitive impairment associated with hippocampal impairment [83–85]. Given that encoding and retrieval of verbal and

visual memory strongly engage left and right hemispheric regions (respectively), including hippocampus [86,87] using tests that are sensitive to detecting deficient hippocampal processing in breast cancer survivors provides a useful diagnostic indicator of basic memory dysfunction. Several longitudinal assessments of patients' verbal and visual memory using the California Verbal Learning Test and the Brief Visuospatial Memory Test-Revised, for example, have identified lower scores relative to pre-treatment baseline and to healthy controls, persisting up to one year post-chemotherapy [88–90]. See Tables 1–3 for test details, and review of verbal and visual memory assessments in breast cancer survivors.

Other neurocognitive assessments of episodic memory employ paired associates learning tasks at encoding, requiring participants to later recognize paired items, words, or spatial contexts, presented during encoding and again during a recognition test [17,91]. Episodic memory involves recollection of details related to the 'what, where, and when' of unique events [92–94]. Using this method of assessment, reduced recognition memory for face-context pairings was observed in chemotherapy treated (Ch+) breast cancer survivors ten years following treatment, indicative of long-lasting memory interference [17]. See 'Neuropsychological Tests (NPT)' column in Tables 1–3 for assessment details. While these verbal and visual memory tasks are well established and validated memory assessments that can provide insight into potential deficits within the episodic memory domain, they are not reflective of the type of complex declarative memory processing required to support the encoding (formation) and recollection of real-life, everyday events and the related semantic information that is an intricate part of human memory for personal experiences [95].

3.1 Complex Declarative Memory Processing and CRCI

Declarative memory, or memory that can be voluntarily called into consciousness, is comprised of both episodic and semantic elements [93]. Semantic memory involves retrieval of facts or general knowledge that is not tied to a specific event, whereas episodic memory involves recollection of details for unique events [92–94]. Both encoding and retrieval of an episodic memory rely heavily on hippocampal engagement. Patients with damage to medial temporal lobe (MTL) structures including

the hippocampus are disproportionately impaired in recalling the episodic components of previously experienced event memories, and will instead provide semantic elements related to the memory [93,96–100]. For example, if prompted to recall a story about a day at their job, an MTL patient could report facts about the company, their position within the company, and their boss' name (preserved semantic memory retrieval), but would be unable to recall a specific event that occurred while working with their boss (impaired episodic memory retrieval).

Even in healthy individuals, the precise episodic elements of a memory are susceptible to forgetting over time whereas the semantic elements of a memory tend to be more stable [93,101,102]. For example, a healthy individual can likely recall their experience of yesterday's staff meeting in vivid detail, including their position in the room, the attendance and appearance of their colleagues, the objects in the meeting room, the order in which their colleagues spoke, and specific phrases (episodic details for the event). If asked to recall a staff meeting from three years ago, that person is likely to remember few episodic details about the meeting, while recalling general, schematic features of the event (i.e., "It was in the conference room. Our boss sat at the front of the table. Each director gave their report"), and semantic information related to the event (i.e., "We have staff meetings every Wednesday at 3:30 PM. The conference room is on the 3rd floor)". Despite this normal loss of memory for episodic details, if given a salient cue at the time of retrieval, healthy individuals can probably access those precise episodic details even after a very long time (i.e., "That was the meeting when Mikki brought pastries from Wisconsin. There were four large, round pastries on the conference table. They tasted very sweet.").

Observations of differential loss of memory details can be accounted for by the Trace Transformation Theory, which posits that episodic memories are consolidated in rich contextual and perceptual detail within the hippocampus. So long as the memory remains accessible, the hippocampus continues to be required for the retrieval of contextually and perceptually detailed elements of the memory. Over time, episodic memories are transformed into less detailed schematic memories that capture the essential features or gist of the original event. Storage and retrieval of

this form of the memory are supported by neocortical regions, with the prefrontal cortex playing a particularly important role. The detailed hippocampus-dependent version, and the transformed schematic version of the memory, can co-exist in the healthy brain, and the available cues at the time of retrieval will direct which version is retrieved [92,95,120]. Regardless of the age of the memory (recent, i.e., yesterday's staff meeting; remote, i.e., staff meeting from three years ago), the hippocampus continues to be engaged when retrieving episodically detailed elements of event memories [120–122].

Given this profile of memory consolidation, it is probable that even subtle hippocampal disruption, such as that resulting from chemotherapy-induced neurogenic suppression or hippocampal atrophy would result in selective impairment in the retrieval of episodic memories. Such results have been identified in preclinical rodent models in which adult hippocampal neurogenesis has been ablated using chemotherapy [60,61] or cranial radiation [39,60,123,124], resulting in impaired context memory which is a measure of episodic-like memory in rodent memory models.

3.2 Autobiographical Memory and CRCI

Autobiographical memory is a unique form of declarative memory that unfolds over time, involves temporal and spatial sequencing of an event, and is comprised of a complex interaction of episodic and semantic elements of a personally experienced event. To recall an autobiographical memory, details that must be accessed from memory stores, reconstructed and elaborated upon during the retrieval process [125,126]. Patients with MTL damage exhibit relative preservation of older autobiographical memories experienced long before hippocampal damage, and a temporal gradient, with memories experienced more recently prior to hippocampal insult being more susceptible to disruption. The remote retrograde memories that are preserved in the presence of hippocampal damage, however, tend to lack episodic specificity, and rather retain a more gist-like and semantic version of the event [100,127,128].

Despite the pervasive reports of memory impairment in those experiencing CRCI and the known susceptibility of the hippocampus to the neurotoxic effects of chemotherapy, only a limited number of studies have investigated autobiographical memory processing in breast cancer survivors. One early investigation using the Autobiographical Memory Task found that Ch+ breast cancer survivors demonstrated reduced ability to produce 'specific' autobiographical memories in response to positive, negative, or neutrally valenced cue words when compared with heathy controls [129]. Rather than retrieving episodic details, Ch+ breast cancer survivors produced overgeneralized memories, thought to result from an impairment in the generative retrieval process that does not reach the elaboration phase required for event-specific memory retrieval [126,130]. The Autobiographical Memory Task [131] used here, however, provides limited insight into potential temporal differences in memory retrieval of personal event memories, as it does not take into account the age of the retrieved memories (recently experienced post-treatment events vs. remotely experienced pre-treatment events), nor does it account for the qualitative content of the retrieved memory beyond classifying it as 'specific', 'general', or a 'non-memory'. This is an important consideration, as impairment resulting from chemotherapy-induced hippocampal neurotoxicity may differentially impair the more specific, episodic components of the recalled event while leaving the more general schematic and semantic components unaffected [105].

Another study assessed both pre- and post-treatment autobiographical memories in breast cancer survivors using the more rigorous TEMPau task, a semi-structured interview that assesses memories for unique events occurring at specific times and places within three lifetime periods: the five years before treatment, the cancer treatment period, and the 12 month post-treatment period [132]. The results identified an overall reduction in autobiographical memory retrieval ability in Ch+ breast cancer survivors, with a specific deficit in retrieval of temporal details. Given the observed deficit in temporal memory processing, it is unfortunate that the study failed to assess potential differences in temporally graded retrograde memory to determine if the more remote (five year old) memories were less impaired than the more recently experienced autobiographical memories. As

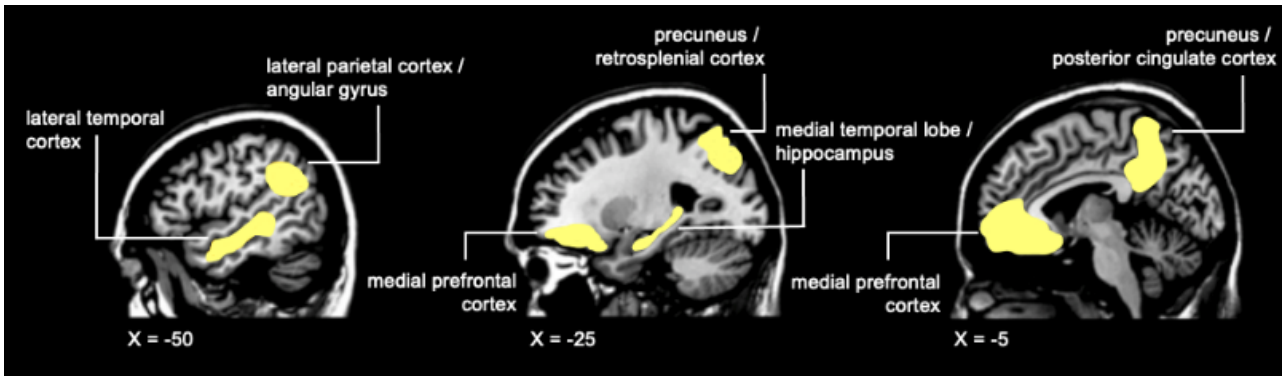
the process of memory transformation and retrieval network reorganization occurs over time, even in healthy individuals [92,95,120,121,133,134], it is plausible that deficits in episodic memory retrieval for complex event memories in Ch+ individuals will be less evident for more remote memories given the natural forgetting of episodic memory details over time, and the reduced reliance on the hippocampus for this type of memory.

Several tests have been developed to probe the qualitative content of autobiographical memories, including the Autobiographical Memory Interview [135] and the Autobiographical Interview [136]. The Autobiographical Interview is a structured memory interview that distinguishes between retrieved episodic details that are unique to the retrieved experience (internal details, i.e., "I was wearing a blue bathing suit and swimming in the cold lake with my brother when he came to visit me last weekend") and semantic aspects of memory (external details, i.e., "It was my favorite bathing suit, I'm a great swimmer, and we used to go to the lake every summer"). The Autobiographical Interview allows for the classification of sub-categories of internal details to identify domains of episodic memory that are susceptible to impairment with a high degree of specificity (perceptual, emotion/thought, time, place, event details).

The Autobiographical Interview has been used to identify episodic memory disturbances in many patient populations involving medial-temporal lobe disruption [128,137–139], and in normal aging [140,141], but has not been used to assess complex event memory processing abilities in chemotherapy-treated breast cancer survivors. The Autobiographical Interview is a powerful tool for detecting subtle episodic memory deficits in the presence of even minor hippocampal dysfunction. A study using the Autobiographical Interview [136] in pediatric brain tumor patients found that chemotherapy and craniospinal radiation were associated with significant impairment in patients' ability to recall specific from personal episodic events experienced following treatment, whereas their ability to retrieve general semantic details from the same events was unimpaired compared to healthy controls. Interestingly, the quality of details recalled for remote, pre-treatment memories was

unimpaired, suggesting that, as with MTL patients, chemotherapy and cranial radiation treatments selectively impair the ability to form new, highly detailed autobiographical memories, while leaving previously established memories unaffected. This pattern of impairment was accompanied by reduced overall volume in the hippocampus, as well as the fornix, the main efferent white matter tract projecting from the hippocampus to the mammillary bodies in the diencephalon [142]. A moderate reduction in volume was also observed in the precuneus, but other nodes of the recollection network (Figure 1), including the medial prefrontal cortex (mPFC), were unaffected. This may account for the preservation of remote retrograde memories, which reorganize and recruit prefrontal cortical regions as the memories age and become less episodically detailed over time [92,95,142,143].

Figure 1. *Regions commonly activated during memory recollection, comprising the recollection networks.*



To date, the few assessments of autobiographical memory performance in breast cancer survivors have identified autobiographical memory as a cognitive domain that is vulnerable to the effects of chemotherapy, yet the measures used to assess the qualitative content of patients' memory have lacked the rigor to objectively assess the subdomains of episodic memory retrieval [106,132]. Critically, they have not accounted for the differential effects of chemotherapy-mediated disruptions along a temporal gradient, including of retrograde, anterograde, and future imagining of autobiographical events. Further, identifying structural and functional differences or changes in the

hippocampus and throughout the recollection network that may be mediating autobiographical memory dysfunction will be essential in identifying therapeutic targets. These are important considerations moving forward, given the susceptibility hippocampal-dependent memory processing to chemotherapy treatments, and its implications for maintaining quality of life in cancer survivors.

4. Neuroimaging Assessments

4.1 Chemotherapy-Induced Structural Changes to Hippocampus and the Temporal Lobes

Within the MTL, and hippocampi specifically, notable structural and functional differences have been observed in breast cancer patients following chemotherapy treatment (Table 1), corroborating findings from pre-clinical studies in rodents [27,49,69]. Early investigations first considered the influence of post-traumatic stress [144], and post-treatment depressive episodes [103] on hippocampal volume in breast cancer survivors. In a series of MRI studies of Japanese breast cancer survivors conducted three years post-treatment (see Table 1 for patient demographic and chemotherapy treatment details), no differences in left or right hippocampal volume, nor overall brain volume, were observed in Ch+ breast cancer survivors who had experienced a first depressive episode following breast cancer treatment [103]. In the same sample, survivors who reported experiencing distressing and intrusive cancer-related recollections for at least one month during the post-treatment interval had marginally smaller left hippocampal volume, relative to survivors with no history of distressing recollections [144]. The quality or content of these recollections was not probed, limiting any conclusions that could be drawn related to the episodic memory performance of these breast cancer survivors. Despite slightly smaller hippocampal volume, standardized tests of delayed verbal or visual memory performance using the Wechsler Memory Scale-Revised suggest that the occurrence of these distressing recollections did not impair general memory processing.

Table 1. *Summary of reports identifying chemotherapy-induced structural differences in the temporal lobes using MRI and associated memory disruption in breast cancer survivors.* Abbreviations: ↑, increase/higher scores; ~, approximately; ↓, reduction/lower scores; = no difference between groups; 6=, not the same/different scores; -, negative correlation; 5FU, fluorouracil; 5^0-DFUR, doxifluridine; AC, CPP + DOX; ACT, DOX + CPP + taxane; AT, DOX + taxane; BLT, Brown Learning Test; BVMT-R, Brief Visuospatial Memory Test-Revised; CAF DOX + CPP + 5FU; CAPE, capecitabine; CD, CPP + DTX; Ch−, breast cancer patients that did not take chemotherapy; Ch+, breast cancer patients that took chemotherapy; chemo, chemotherapy treatment; CMF, CPP + MTX + 5FU; CNS-VS, computerized neurocognitive assessment vital signs; CPP, cyclophosphamide; CVLT, California Verbal Learning Test; DOX, doxorubicin; DTX, docetaxel; EC, epirubicin and cyclophosphamide; ET, endocrine therapy; FEC-D, 5FU + CPP + epirubicin + DTX; GM, gray matter; GMD, gray matter density; HC, healthy controls; HPC, hippocampus; HCFU, carmofur; HVLT, Hopkins Verbal Learning Test; MDE, major depressive episode; MF, MTX + 5FU; MTX, methotrexate; mo, months; n, sample size; NPT, Neuropsychological Tests; ParaHPC, parahippocampal; Peri-M., perimenopausal; postchemo, postchemotherapy treatment; Post-M., postmenopausal; Pre-M., premenopausal; PTX, paclitaxel; RAVLT, Rey Auditory Verbal Learning Test; RT, radiation therapy; STG, superior temporal gyrus; t1, testing session 1; t2, testing session 2; t3, testing session 3; TAC, CPP + DOX + docetaxel; TBV, total brain volume; UFT, tegafur/uracil; WMS-R, Wechsler Memory Scale-Revised; WM, white matter; yr, year(s).

References	Sample	Age	Tumor Stage	Menopausal Status	Treatment	Timepoints	NPT	NPT Results	Imaging Results
Inagaki et al. [103]	Ch + MDE (*n* = 17), Ch+ (*n* = 51)	18–55	0–III	Post-M. (*n* = 10 Ch + MDE, *n* = 27 Ch+)	Chemo, ET, surgery	6 mo postsurgery (t1)	WMS-R: immediate and delayed verbal and visual memory tasks	=verbal and visual memory for both groups	=left and right HPC volume for Ch + MDE and Ch+
Yoshikawa et al. [104]	Ch+ (*n* = 44), Ch− (*n* = 31)	~48	0–I	Post-M. (*n* = 27 Ch+, *n* = 8 Ch−)	Chemo (CMF, AC, CAF, CPP, MF, 5FU, HCFU, or doifluridine), ET, RT, surgery	~3.5 yr postchemo (t1)	WMS-R: immediate and delayed verbal and visual memory tasks	=verbal and visual memory for both groups	=HPC volume between Ch+ and Ch− and between different chemotherapy regimens
Ferguson et al. [105]	Ch+ (*n* = 1), HC (*n* = 1) monozygotic twins	60	II	-	Chemo (TAC), ET	22 mo postchemo (t1)	verbal memory: CVLT, Craft stories	=verbal memory for both twins	↑ WM lesion volumes and hyperintensities for Ch+ than HC
Inagaki et al. [106]	Ch+, Ch−, HC (*n* = 51–55/ group)	18–55	0–I	Post-M. (*n* = 40 Ch+, *n* = 20 Ch−, *n* = 16 HC)	Chemo (AC, CMF, EC, PTX, 5FU, 5^0-DFUR, HCFU, or UFT), ET, RT	1 yr postsurgery (t1) and 2 yr after t1 (t2)	WMS-R: immediate and delayed verbal and visual memory	-	↓ GM and ↓ WM in paraHPC, prefrontal, precuneus at t1 for Ch+ than Ch−; = GM and WM at t2
McDonald et al. [107]	Ch+ (*n* = 17), Ch− (*n* = 12), HC (*n* = 18)	~50	0–III	-	Chemo (CPP + DOX, ACT, or AC), ET, surgery	Baseline (t1), 1 mo (t2) and 1 yr postchemo (t3)	-	-	= GM at t1; ↓ GM bilateral paraHPC, STG at t2 than t1 and MTL at t3 than t1 for Ch+ than HC
Koppelmans et al. [13]	Ch+ (*n* = 177), HC (*n* = 368)	50–80	-	-	Chemo (CMF)	~21 yr postchemo (t1)	-	-	↓ GM, ↓ TBV, =WM, =left HPC volume for Ch+ and HC
Conroy et al. [108]	Ch+ (*n* = 24), HC (*n* = 34)	49–71	I–III	-	Chemo (AC, ACT, CAF, AT, CMF, CMF + CAF, taxane, ACT+ CAPE, or taxane + CAPE)	~6.4 yr postchemo (t1)	verbal memory: RAVLT, story recall, BLT	↓verbal memory for Ch+ than HC	↓ GMD in left temporal lobe for Ch+ than HC.

Kesler et al. [109]	Ch+ (*n* = 42), HC (*n* = 35)	~55	I–III	Post-M. (*n* = 33 Ch+, *n* = 18 HC)	Chemo (DOX + CPP, DOX + PTX, CPP + 5FU + PTX, or CPP + 5FU+ MTX), ET, RT	~5 yr postchemo	verbal memory: HVLT	↓ HVLT delayed recall for Ch+ than HC	↓ bilateral HPC volume for Ch+ than HC
Lepage et al. [110]	Ch+ (*n* = 19), HC (*n* = 19)	~50	I–III	Menstruating, peri-m, post-m (*n* = 2–9/group)	Chemo (FECD, CD, or CPP + DOX), surgery	baseline (t1), 20 days (t2) and 1.5 yr postchemo (t3)	verbal memory: HVLT, CNS-VS-Verbal Memory Index; visual memory: BVMT-R, CNS-VS-Visual Memory Index	↓ NPT scores over time (nonsignificant) for both groups	↓ GM volume in temporal regions from t1 to t2 for Ch+ compared to HC, = GM at t3 between both groups
Apple et al. [73]	Ch+ (*n* = 16), HC (*n* = 18)	18–45	I-IV	Pre-M.	Chemo (ACT), ET	6–18 mo postchemo (t1)	episodic memory: Picture Sequence Memory Test	↓episodic memory for Ch+ than HC	↑inward deformation in bilateral HPC, ↓HPC volume for Ch+ than HC

Secondary analyses of these data, including the addition of a sample of non-chemotherapy-treated (Ch−) breast cancer survivors, failed to find any difference in hippocampal volume, whole brain volume, or any differences in delayed verbal of visual memory performance between Ch+ and Ch− survivors [104]. Given that scans and cognitive assessment were performed three years following treatment, the study suggested that a longitudinal approach including earlier timepoints may be required to detect potential chemotherapy-induced impairment in hippocampal volume and morphology.

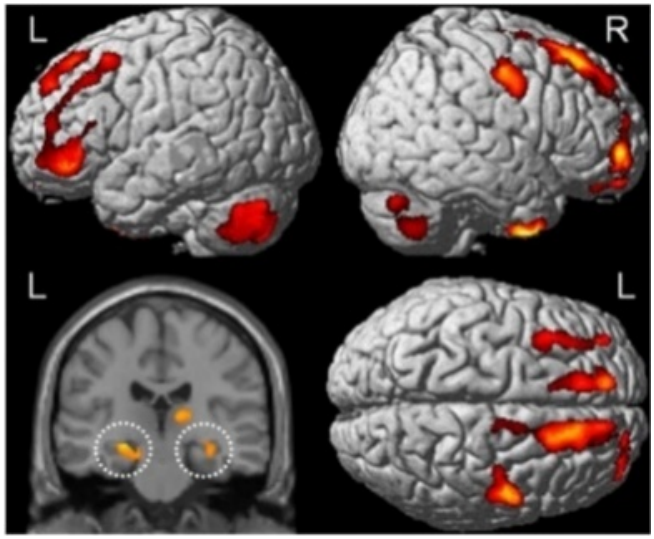
Accordingly, structural imaging of both Ch+ and Ch− breast cancer survivors approximately one year following surgery and chemotherapy treatment identified smaller gray matter and white matter volumes within the parahippocampus, adjacent to the hippocampus, and recollection network regions including the prefrontal cortex and precuneus in Ch+ survivors [106]. Smaller gray matter volume within these regions was not evident three years post-treatment [106], consistent with their earlier null findings in a sample of survivors after three years [104]. See Table 1 for a summary of MRI studies finding chemotherapy-related disruptions in the hippocampus and temporal lobes.

Since these early studies highlighting the need for a more longitudinal approach to monitoring chemotherapy-induced neural alterations, many subsequent MRI studies of brain volume and morphology have identified structural differences in white matter tracts and gray matter volumes across various brain regions in Ch+ breast cancer survivors [13,17,105,109,145,146].

The first MRI study to track longitudinal changes in gray matter volume across the whole brain using voxel-based morphometry (VBM) prior to, and following, chemotherapy treatment found significantly lower gray matter volumes within the bilateral hippocampus, parahippocampus, superior temporal gyrus, and regions in the frontal lobes, cerebellum, and thalamus just one month following treatment (Figure 2). Widespread density reductions were largely transient, with recovery of gray matter volume observed in the superior temporal regions one year following treatment in these same patients, though reduced density within the MTL and frontal lobes largely persisted after one year [107]. Gray matter density reductions were not

observed in Ch− breast cancer survivors, suggesting that the persistent gray matter density deficits were not the result of cancer-related disturbances, but rather due to chemotherapy-induced neurotoxicity. A follow-up study incorporating fMRI performed 3–10 years post-treatment, confirmed lower gray matter densities within the left temporal lobe, and hypoactivation within the left middle temporal gyrus, while performing a working memory n-back task. No functional assessments with long-term memory tasks were performed, but the authors report impaired delayed memory scores on the Rey Auditory Verbal Learning Test in Ch+ breast cancer survivors. This memory deficit may be mediated, in part, by the observed left temporal lobe structural and functional disruption in Ch+ survivors [108].

Figure 2. *Voxel-based morphometry identified gray matter density declines (warm colours) between pre-treatment baseline and 1-month post-chemotherapy, notably within bilateral hippocampal and parahippocampal regions (white dashed circles).*



A subsequent longitudinal study using VBM to assess gray matter volume changes one month, and one year post-treatment identified structural changes in the temporal lobes relative to pre-treatment baseline measures. A significant decline of volume in right hippocampus and right superior and middle temporal gyri was evident as early as one month following chemotherapy, and persisted one year post-treatment. Surprisingly, verbal and visual memory showed only modest impairment over time, despite the notable declines in temporal lobe gray matter [110].

A sample of Ch+ breast cancer survivors imaged between 1 and 12 years post-treatment revealed persistent effects of treatment on hippocampal volumes, with smaller left hippocampal volumes and inferior performance on the Hopkins Verbal Learning Test memory task relative to controls. In a sub-set of sampled patients, smaller left hippocampal volumes were associated with increased circulating pro-inflammatory cytokine expression of IL-6 and TNF-α [109]. While speculative, the cause of volume reductions within the detectable by MRI are likely associated with underlying cellular and molecular disturbances targeting the hippocampus, including suppressed neurogenesis, and dendritic atrophy [26,28].

4.2 Functional Specialization Along the Hippocampal Long-Axis and Implications for Memory Performance Following Chemotherapy

Chemotherapy-treated women within 18 months of completing treatment had significantly altered hippocampal morphology, with bilateral inward deformation predominantly within the anterior portion of the hippocampal long-axis, and smaller overall hippocampal volume. This deformity was associated with poorer episodic memory performance on the Picture Sequence Memory Task and with self-reported cognitive difficulties [73].

Hippocampal deformity within the anterior region may differentially impact memory processing, as the hippocampus is functionally specialized along its long axis and has unique structural connectivity in its anterior and posterior regions. The anterior hippocampus (analogous the ventral hippocampus in rodents) has connections with the ventromedial prefrontal cortex (vmPFC), and is associated with the processing of schematic memories [92,147]. The posterior hippocampus (analogous to dorsal hippocampus in rodents) [148] is thought to be involved in processing more fine-grained details that characterize vivid and perceptually detailed episodic memories [92,147].

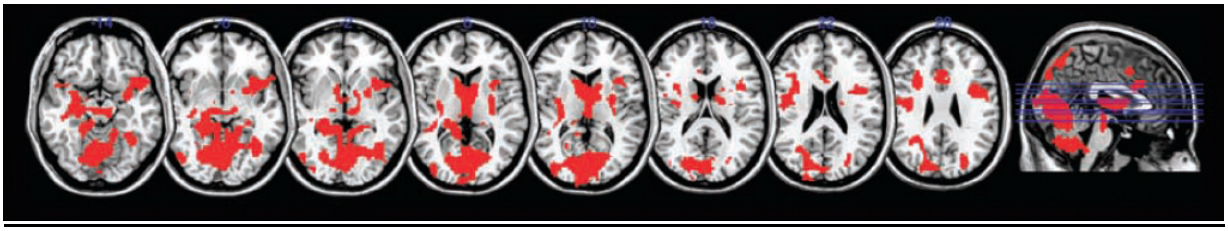
In their study of autobiographical memory in breast cancer survivors 18 months post-treatment, Bergouignan and colleagues (2011) observed a specific deficit in recalling temporal details within autobiographical memory [132]. They also found reduced posterior hippocampal volume, which likely underlies the deficit in episodic memory retrieval, given the putative role of

posterior hippocampus in processing fine-grained spatio-temporal aspects of episodic memory [147,149,150]. The posterior hippocampus has also been shown to be activated during autobiographical memory elaboration which requires the production of perceptually detailed elements of the memory [126], while connectivity between anterior hippocampus and vmPFC regions is more strongly engaged during the initial general construction phase of autobiographical memory retrieval [125,126,151,152]. These regional specializations in autobiographical memory processing may also account for the overgeneralized autobiographical memories reported by Bergouignan et al. [132], in the case of posterior hippocampal atrophy or shrinkage. Taken together, these findings suggest that chemotherapy-induced regional disruptions within the hippocampus may be indicative of the types of memory dysfunction a patient is likely to develop.

4.3 Chemotherapy-Induced Functional Disruptions in the Temporal Lobes and Broader Recollection Network

An early study of fMRI neural dynamics and memory performance identified significantly greater activity across broad regions of the recollection network (Figure 1) in Ch+ breast cancer survivors performing a delayed verbal memory recognition task. Hyperactivity was observed in left hippocampus, bilateral parahippocampus gyri, right superior temporal gyrus, bilateral precuneus, right cingulate gyrus, and throughout several regions of the frontal lobes (Figure 3) [111]. The recognition accuracy of Ch+ breast cancer survivors was comparable to healthy controls. These results suggest that successful memory processing following chemotherapy is supported by compensatory over-recruitment of key nodes of the temporal lobes and the recollections network, reflective of inefficient neural processing. See Table 2 for a summary of fMRI studies showing chemotherapy-related disruptions in the hippocampus and temporal lobes during performance of memory tasks.

Figure 3. *SPM analyses identified hyperactivity (warm colours) during accurate delayed verbal memory recognition in Ch+ breast cancer survivors compared to healthy control.* Adapted from Kesler et al. [111].



While network hyperactivity may reflect a compensatory response supporting memory performance following chemotherapy treatment, network hypoactivity has been associated with poor memory performance. A study of fMRI neural dynamics in Ch+ and Ch− breast cancer survivors conducted ten years after the completion of a high-dosage chemotherapy treatment found long-lasting hypoactivation of the parahippocampal gyrus in Ch+ survivors during encoding of a paired associates episodic memory task in which participants were shown a series of combinations of faces and contexts (i.e., a living room). During a subsequent recognition task in which participants had to judge the accuracy of the face-context pairings after a delay of several minutes, Ch+ breast cancer survivors had lower recognition accuracy scores than Ch− survivors [17]. This study provided support for the persistent altered neural dynamics within the MTL associated with chemotherapy treatment by accounting for cancer-related complications also experienced by the Ch− survivors. These data strongly suggest that altered neural dynamics with the MTL mediate the occurrence of episodic memory impairment, and can account for the high incidence of persistent memory loss in Ch+ breast cancer survivors.

Subsequent longitudinal investigation using this same paired associates task in Ch+, Ch−, and healthy controls [91] identified no differences between groups during a pre-treatment baseline assessment, or during a 6-month post-treatment assessment on the face-context memory recognition task. While all groups showed robust activation of the hippocampus during the recognition task, no notable differences were seen between Ch+ and Ch− or healthy controls at the 6-month post-treatment period. When compared with their earlier findings [18] which find long-term disruption of parahippocampal processing ten years post-treatment, these findings suggest that identifying disruptions within the retrieval network in response to chemotherapy may develop over time. Their findings highlight the importance of tracking the development of neural

dynamic disruptions longitudinally at repeated time points in patients to better understand the temporal profile of the development and persistence of CRCI.

Another study involving longitudinal tracking of functional networks in breast cancer survivors identified chemotherapy-induced changes in a widespread network of regions while performing a verbal memory task one month following chemotherapy [112]. Relative to patients' pre-treatment baseline, network hypoactivity was observed in the right superior temporal gyrus, bilateral insula, and left inferior orbitofrontal gyrus, during recognition testing. Differences in functional network activity during the recognition memory task were also observed between Ch+ survivors and healthy controls, most notably in the superior and middle temporal gyrus, the left insula and superior temporal pole, and several frontal regions (Table 2). No deficits in verbal recognition memory performance were evident in Ch+ breast cancer survivors when compared to their baseline accuracy levels, or when compared to healthy control performance, despite network hypoactivity during the task. Thus, during a recognition task with relatively low cognitive demands, network hypoactivity did not result in detectable deficits in performance.

Interestingly, in participants reporting high levels of fatigue, the hippocampus was more highly activated in Ch+ patients than controls, suggesting that successful recognition memory when highly fatigued requires extra engagement of hippocampal processing to support cognitive performance.

A preliminary study investigated eye-tracking during fMRI scanning in Ch+ patients and healthy controls while they performed the Picture Sequence Memory Test, an established spatial recognition memory task that is sensitive to hippocampal dysfunction [153]. While Ch+ patients were not impaired on the recognition task during scanning, they showed reduced eye-movement based discrimination, a measure of implicit memory (non-declarative memory) for the task. Reduced eye-movement discrimination was associated with hippocampal hypoactivation and smaller hippocampal volume, compared to control levels [154]. The connection between the observed implicit memory deficit and hippocampal abnormalities in Ch+ patients is not clear, as implicit memory is not considered to be dependent on the hippocampus [155–157].

Table 2. *Summary of reports identifying chemotherapy-induced functional differences in the temporal lobes and memory disruption in breast cancer survivors using task-based fMRI.* Abbreviations: ↑, increase/higher scores; ~, approximately; ↓, reduction/lower scores; = no difference between groups; 6=, not equal/different scores; +, positive; 5FU, fluorouracil; AC, CPP + DOX; ACT, DOX + CPP + taxane; AT, DOX + taxane; BCP, breast cancer patients; CAF, 5FU + CPP + DOX; CAPE, capecitabine; Ch−, breast cancer patients that didn't take chemotherapy; Ch+, breast cancer patients that took chemotherapy; Chemo, chemotherapy treatment; CMF, CPP + MTX + 5FU; CPP, cyclophosphamide; CTC, CPP + thiotepa + carboplatin; CVLT, California Verbal Learning Test; DOX, doxorubicin; DTX, docetaxel; EBPM, event-based prospective memory; ET, endocrine therapy; FC, functional connectivity; FEC, 5FU + epirubicin + CPP; FFA, fusiform area; fMRI, functional magnetic resonance imaging; HC, healthy controls; HPCn, hippocampal network; mo, months; MTG, medial temporal gyrus; n, sample size; NPT, neuropsychological tests; PA, paired associates; paraHPC, parahippocampal; Peri-M., perimenopausal; PFC, prefrontal cortex; PHG, parahippocampal gyrus; postchemo, postchemotherapy treatment; Post-M., postmenopausal; Pre-M., premenopausal; pTG, posterior temporal gyrus; PTX, paclitaxel; RT, radiation therapy; RWCR, novel recognition without cued recall; STG, superior temporal gyrus; t1, Testing session 1; t2, testing session 2; TBPM, time-based prospective memory; TEC, DTX + CPP + epirubicin; TG, temporal gyrus, WMS-R, Wechsler Memory Scale-Revised; yr, year(s).

References	Sample	Age	Tumor Stage	Menopausal Status	Treatment	Timepoints	NPT	NPT Results	Imaging Results
Kesler et al. [111]	Ch+ (*n* = 14), HC (*n* = 14)	40–65	metastatic (*n* = 8), locally advanced (*n* = 6)	-	Chemo (CMF, or ACT), ET, RT	>6 mo postchemo (t1)	Verbal declarative memory encoding and recall task in fMRI	=verbal declarative memory for both groups	↑ right STG activation extending into paraHPC and left HPC during the verbal declarative encoding and recall task for Ch+ than HC
de Ruiter et al. [17]	Ch+ (*n* = 19), Ch− (*n* = 15)	~57	I-III	-	Chemo (FEC, or CTC), ET, RT, and surgery	~2 (t1) and 9 yr postchemo (t2)	verbal memory: CVLT; visual memory: WMS-R visual reproduction test; episodic memory: PA in fMRI	t1 to t2: ↓ PA for Ch+ than Ch−; ↓ visual and verbal memory for Ch+ than HC	↓ right PHG and MTG activation during PA task for Ch+ than Ch−
Lopez-Zuinini et al. [112]	Ch+ (*n* = 21), HC (*n* = 21)	31–64	I-III	Peri-M. (*n* = 2–4/group), Post.M. (*n* = 9–10/group)	Chemo (CPP + DOX, CPP + DTX, 5FU + CPP+ DTX + hepirubicin+ epirubicin or 5FU, TEC), surgery	baseline (t1), and 1 mo postchemo (t2)	verbal memory: verbal word list learning in fMRI	=verbal word learning for both groups	↓ activation in right STG, bilateral insula, and left inferior orbitofrontal gyrus during the verbal list learning task for Ch+ than HC
Apple et al. [113]	Ch+ (*n* = 16), HC (*n* = 18)	18–45	-	Pre-M.	Chemo, ET	~18 mo postchemo (t1)	episodic memory: Picture Sequence Memory Test and RWCR in fMRI	↓ episodic memory for Ch+ BCP than HC	↑ HPC FC in the left cuneus, lingual, precuneus, and right middle frontal gyrus during RWCR for Ch+ than HC

In later task-based functional connectivity analyses of these data, Apple and colleagues (2018) identified strong intra-hippocampal connectivity for both Ch+ patients and controls, but Ch+ patients showed evidence of enhanced hippocampal connectivity with the left cuneus and precuneus, lingual gyrus, and right middle frontal gyrus compared to healthy control levels. Higher hippocampal connectivity with the precuneus was associated with higher reports of subjective cognitive concern scores in Ch+ patients, suggesting that hyper-connectivity within these nodes of the recollection network may be compensatory in supporting normal memory performance and needed to overcome anxiety-induced behavioural deficits associated with subjective concern over one's cognitive abilities [113].

4.4 Recollection Network and Default Mode Network (DMN) Irregularities: Implications for Chemotherapy-Related Memory Impairments and Deficits in Episodic Future Thinking

Many of the neural regions identified as comprising the recollection network overlap with nodes of the default mode network (DMN). The DMN is a collection of brain regions that are active when engaged in passive, internally focused cognition (mind wandering) or during a resting state [158–162]. During rest or mind wandering, the brain engages in recollection and in future thinking (planning, imagining) [137,163]. Neuroimaging studies have shown that both future thinking and recollection engage the same core network of brain regions including the mPFC, lateral and medial temporal regions (hippocampus and parahippocampal cortex), and lateral and medial parietal regions (precuneus and retrosplenial cortex) (Figure 1), suggesting a similar underlying neural mechanisms mediating past and future memory processing [137,163–167]. This common DMN/recollection network engaged during mind wandering is an adaptive process that has been proposed to integrate and recombine associations from experiences stored in episodic memory to predict possible future situations in a process of 'constructive episodic simulation' [137,168,169].

Prospective memory is a form of future thinking that involves planning and remembering to execute a task in the future [170]. It is mediated largely by regions within the frontal lobes (notably Brodmann Area 10) [171,172] and MTL [170,173], and is sensitive to disruption following

chemotherapy [116,174,175]. Episodic future thinking is a complex form of prospective thinking which involves imagining or mentally projecting oneself into the future in order to pre-experience events. This process relies on similar cognitive processing and neural network activation involved in episodic recollection [176–178]. Given the overlap in functional activity for past and future episodic thinking, and observations of deficits in future imagining in individuals with MTL damage [128,135,178–181], it is plausible that deficits in episodically-detailed future thinking may occur following chemotherapy.

It is unsurprising that individuals with damage or dysfunction within the MTL, including key nodes of the recollection and DMN networks, engage in episodically impoverished mind-wandering. Mind wandering occurs in individuals with MTL disruption, but unlike healthy adults who report thoughts and recollections about the past, and future imagining during mind wandering, individuals with MTL damage report more semantically based thoughts about the present. This reflects an inability to engage hippocampally-mediated recollective processing required for episodic memory retrieval or episodic future thinking [182].

Bruno and colleagues [114] were the first to identify brain-wide resting state network irregularities in Ch+ breast cancer survivors. Their analysis of resting state activity identified lower global clustering scores in patients, which is indicative of inefficient neurotransmission between hub regions. Hubs are highly interconnected neural nodes that enable efficient network neurotransmission. They also identified several network hubs in the superior temporal gyrus, hippocampus and amygdala in controls that were not evident in breast cancer survivors during the resting state. Inefficient regional hub connectivity and global network processing may underlie reports of hyper-activity during cognitive task performance in cancer survivors, as the network must work harder to communicate across regions due to reduced direct connectivity [111,113]. The network connectivity inefficiencies identified at rest were associated with lower delayed verbal memory scores, and subjective reports of memory difficulties in this sample of Ch+ breast cancer survivors [114]. See Table 3 for a summary of resting state fMRI studies finding chemotherapy-related disruptions in the hippocampus and temporal lobes.

Table 3. *Summary of reports identifying chemotherapy-induced functional differences in the temporal lobes during resting state fMRI in breast cancer survivors.* Abbreviations: ↑, increase/higher scores; ~, approximately; ↓, reduction/lower scores; = no difference between groups; 6=, not the same/different scores; >, above; 5FU, Fluorouracil; ACT, DOX + CPP + taxane; ADM, adroamycin; ADMN, anterior default mode network; ALFF, amplitude of low-frequency fluctuation; AVLT, Auditory Verbal Learning Test; BCP, breast cancer patients; Ch−, breast cancer patients that didn't take chemotherapy; Ch+, breast cancer patients that took chemotherapy; chemo, chemotherapy treatment; CN, Central network; CPP, cyclophosphamide; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; DOX, doxorubicin; DTX, docetaxel; ET, endocrine therapy; FC, functional connectivity; HC, healthy controls; HVLT, Hopkins Verbal Learning Test; HPC, hippocampus; ITG, inferior temporal gyrus; LFPN, left frontoparietal network; mo, months; MTG, middle temporal gyrus; MTX, methotrexate; n, sample size; NPT, Neuropsychological Test; ParaHPC, parahippocampal; pCC, posterior cingulate cortex; PDMN, posterior default mode network; postchemo, postchemotherapy treatment; Post-M., postmenopausal; Pre-M., premenopausal; pSTG, temporal pole of superior temporal gyrus; PTX, paclitaxel; ReHo, regional homogeneity; RFPN, right frontoparietal network; rs-fMRI, resting state functional magnetic resonance imaging; RT, radiation therapy; SRN, Self-referential network; STG, superior temporal gyrus; t1, Testing session 1; t2, testing session 2; t3, testing session 3; TAC, DTX + ADM + CPP; TC, DTX + CP; TEC, DTX + CPP + Epirubicin; VN, visual network; WDT, Auditory verbal learning memory; yr, year(s).

References	Sample	Age	Tumor Stage	Menopausal Status	Treatment	Timepoints	NPT	NPT Results	Imaging Results
Bruno et al. [114]	Ch+ (*n* = 34), HC (*n* = 27)	40–74	I-IV	Post- and Pre-M.	Chemo (ADM + CPP + PTX, CPP + MTX + 5FU and ADM + CPP or, CPP + MTX + 5FU), ET, RT	~5 yr post-treatment (t1)	verbal memory: HVLT	=HVLT immediate, ↓HVLT delayed for Ch+ than HC	↓ global and regional network measures in bilateral STG for Ch+ than HC; ↑network hubs in bilateral STG and left HPC for HC than Ch+
Tao et al. [115]	Ch+ (*n* = 33), HC (*n* = 31)	26–52	I-III	-	Chemo (DOX, CPP, PTX), surgery	-	-	-	↓ FC in the DMN for Ch+ compared to HC
Cheng et al. [116]	Ch+ (*n* = 34), HC (*n* = 31)	~50	-	-	Chemo (DOX, 5FU, CPP, or PTX)	-	prospective memory: EBPM, TBPM	↓ EBPM, TBPM for Ch+ than HC; =scores between HC and Ch−	↑ FC between HPC seed and bilateral vmPFC, dlPFC, inferior and superior parietal lobules, pCC, and precuneus for Ch+ than HC
Chen et al. [117]	Ch+ (*n* = 16), HC (*n* = 14)	>60	I-III	-	Chemo (TC or other), surgery	baseline (t1), 1 mo postchemo (t2)	episodic memory: Picture Sequence Memory Test	=NPT scores for Ch+ and HC across t1 and t2	↑ ALFF from t1 to t2 in a single cluster including bilateral subcallosal gyri and right anterior cingulate gyrus for Ch+ compared to HC; =rs-fMRI from t1 to t2 for Ch+ and HC
Feng et al. [118]	Ch+ (*n* = 29), HC (*n* = 25)	30–50	I-III	Pre-M. (*n* = 17–20/group), Menopausal (*n* = 8–9/group)	Chemo (ACT, TEC), surgery	baseline (t1), 1 week postchemo (t2)	verbal memory: AVLT	↓ AVLT from t1 to t2 for Ch+ than HC	↑ FC between left anterior HPC and left MTG and STG, and between the right posterior HPC and left STG for Ch+ compared to HC
Feng et al. [119]	Ch+ (*n* = 7), HC (*n* = 19)	35–55	I-III	Pre-M. (*n* = 11/group), Menopausal (*n* = 6–8/group)	Chemo (ACT, TEC), ET	baseline (t1), 1 week (t2) and 6 mo postchemo (t3)	verbal memory: WDT	↓ WDT from t1 to t3 for Ch+ than HC	↓ FC in ADMN, PDMN, LFPN, RFPN, SRN, CN from t1 to t3 for Ch+ than HC

Modelling analyses by Kesler and colleagues (2017) found that pre-treatment resting state network dynamics can be used to predict the development of cognitive impairment in the first year following chemotherapy treatment, suggesting that irregularities in network dynamics are already detectable at the time of disease onset, and are further exacerbated by chemotherapy treatment [183]. Using multi-voxel pattern analyses (MVPA) of 19 seed regions within the DMN during a resting task, Kesler et al. (2013) were able to distinguish Ch+ breast cancer survivors from Ch−, from healthy controls with a high degree of accuracy [184]. MVPA is a neuroimaging technique that uses an individual's pattern of neural activity during a task or during rest to predict their cognitive state or condition [185]. MVPA was unable to distinguish Ch− breast cancer patients from healthy controls above chance levels using these same regions of interest, suggesting that differences in DMN dynamics between groups was associated with chemotherapy treatment, and not due to the disease state itself.

Seed-based connectivity analyses during a resting state task by Cheng and colleagues [116] identified enhanced hippocampal functional connectivity between regions of the DMN including bilateral vmPFC and dlPFC, inferior and superior parietal lobules, pCC, and precuneus in Ch+ breast cancer survivors relative to healthy controls. They also identified prospective memory impairments associated with hippocampal hyper-connectivity in Ch+ breast cancer survivors relative to controls, and compared to pre-treatment prospective memory performance levels for both event and time-based tasks. Their findings suggest that this altered hippocampal connectivity with the rest of the DMN underlies prospective memory difficulties observed in this same sample of breast cancer survivors [116]. Similarly, post-treatment increases in resting state hippocampal connectivity was identified along the hippocampal long-axis relative to the pre-treatment connectivity pattern [118]. Long-axis connectivity changes during rest were associated with poorer auditory memory scores in Ch+ relative to controls.

Post-treatment perturbations in DMN connectivity patterns have been proposed as a potential biomarker of chemotherapy-induced neurotoxicity, and assessment of patient's resting state network dynamics may be a useful non-invasive diagnostic tool for identifying those requiring

cognitive intervention post-treatment [186]. While this review focused on resting state network disruption involving the temporal lobes and its relation to the recollection network and memory processing, it should be noted that disrupted resting state network connectivity in Ch+ breast cancer survivors has also been widely reported using functional connectivity analyses of non-temporal nodes of the DMN, most notably within the frontal and parietal lobes, and accompanied by working memory and executive function impairments [115,116,119,187,187–189].

5. Other Contributing Psychosocial Factors Affecting Memory Performance

Fatigue, anxiety, stress, and other psychosocial factors likely influence cognitive performance, and confound interpretations of performance on standard neurocognitive tests [112,113,190]. Observations in breast cancer patients prior to chemotherapy reveal that disease onset alone is sufficient to induce several physiological changes which may account, in part, for observed cognitive impairments. These changes include disputations in functional network dynamics in frontal and parietal regions [183], and related impairments in executive function, working memory [183,191,192], response inhibition [191], and planning [91] in early-stage breast cancer patients.

Self-perceived impairments in memory are a common complaint following chemotherapy treatment [6,146,193]. Subjective accounts are an important indicator of an individual's perceived cognitive abilities. However, for complex event memories, there is evidence that an individual's confidence in the quality of their memory is not an especially reliable measure of its accuracy [194–196]. In this case, perceived memory difficulties may rather reflect other psychosocial behavioural conditions such as stress, depression, or anxiety [197,198].

Following a cancer diagnosis, approximately 14% of patients develop cancer-related post-traumatic stress disorder [199,200]. There is evidence that retrieval of autobiographical events surrounding the time of diagnosis is altered in recently diagnosed patients [201,202]. This alteration, or distortion, of self-related event memories also intrudes into episodic future thinking, with a bias towards negative affective details when thinking about the future. High levels of

anxiety associated with a diagnosis have been found to impair the emotional content of autobiographical memory retrieval, even prior to the initiation of chemotherapeutic intervention, identifying autobiographical memory as a cognitive domain that is highly susceptible to distortion in breast cancer patients [203].

6. Recommendations and Conclusions

This review and commentary on the current state of the memory-related literature in the field of CRCI has identified a gap in our knowledge of the impact of chemotherapy on complex episodic memory processing and alterations to the recollection network. In light of the susceptibility of the hippocampus to chemotherapy-induced neurotoxicity, and the critical role of the hippocampus in episodic memory processing, it is surprising that there has been so little investigation of complex event and autobiographical memory processing in cases of CRCI. A multidisciplinary approach that combines complementary assessments of lab-based neurocognitive episodic memory performance, with more complex real-life event memory assessments (e.g., autobiographical memory) is needed to fully characterize the specific memory domains affected by cancer onset and chemotherapy treatments.

While chemotherapy-related suppression of neurogenesis is a leading candidate underlying the memory disruptions and hippocampal functional impairment, other physiological factors likely also contribute to these deficits, including white-matter degradation in the hippocampus and throughout other regions of the recollection network [145], pro-inflammatory cytokine [23,184] and microglial activation [26,27], among others. Multi-modal and longitudinal neuroimaging assessments are required to better capture structural and functional changes that develop and persist over time. These findings are essential to identifying the underlying mechanisms that contribute to cognitive impairments within the domains of complex event memory processing, and future thinking. The limited investigations to date highlight the need for systematic investigation of this cognitive domain, and further review of the medial-temporal lobe and recollection network alterations associated with CRCI-induced memory disturbances in cancer survivors.

Investigation of these cognitive domains in CRCI are still in their infancy. Given the importance of autobiographical memory to a person's personal history, sense of identity, and ability to plan for the future, an under-appreciation of how this memory domain may be impaired by standard cancer treatments, has the effect of diminishing the negative experiences of breast cancer survivors, and neglecting cognitive problems that could benefit from intervention strategies.

7. References

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CHAPTER 3

Persistent Adverse Effects of Cancer Treatments on Mental Health, Fatigue, and Sleep Disturbances in Breast Cancer Survivors

Meenakshie Bradley-Garcia[1], Annick F. N. Tanguay[1], Melanie J. Sekeres[1]

[1]School of Psychology, University of Ottawa, Ottawa, Ontario, Canada

Authors note

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Abstract

Breast cancer is the most diagnosed cancer worldwide, affecting one in four women diagnosed with cancer. Cancer treatments, particularly chemotherapy, can adversely impact mental health, contributing to increased stress, anxiety, depression, fatigue, and poor sleep quality. This study investigated the long-term psychological effects of cancer treatment among breast cancer survivors and explored interactions between these factors. We recruited Canadian women aged 30 to 65 with a history of breast cancer who were at least 6-months post-treatment (n = 49) and age-matched control participants (n = 44). Participants provided demographic and health information and completed online questionnaires assessing stress, depression, trait and state anxiety, fatigue, sleep quality, and physical activity. Breast cancer survivors reported significantly higher levels of stress (p = .004), depression (p < .001), state anxiety (p = .003), trait anxiety (p = .02), fatigue (p < .001), as well as poorer sleep quality (p < .001) compared to non-cancer controls. Physical activity levels and leisure-time exercise did not differ between groups (p = .13 and p = .17, respectively). While physical activity was not significantly correlated with mental health factors in either group (p's > .05), most mental health factors were correlated with each other in both groups (p's < .05). Our findings enhance understanding of the long-term mental health effects of cancer treatment in breast cancer survivors, providing strong evidence that breast cancer survivors continue to experience significant psychological challenges – including stress, anxiety, depression, fatigue, and sleep disturbances. Given these persistent challenges, it is critical to incorporate comprehensive mental health assessments into cancer survivorship plans to identify psychological concerns and inform treatment strategies that address the interconnectedness of these issues.

Keywords: breast cancer, depression, anxiety, fatigue, sleep disturbances, exercise, stress, post-treatment, chemotherapy, survivorship

1. Introduction

Breast cancer is the most diagnosed cancer among women worldwide, affecting one in four women diagnosed with cancer (1). Treatment decisions for breast cancer are determined by several factors, including the tumor size, location, stage, and estrogen and progesterone hormone receptor status (2). Standard treatment options include surgery, radiation, chemotherapy, and hormonal therapy (2). Although advancements in prevention strategies, screening, and treatment have significantly improved survival rates (2,3), they have also increased awareness of treatment-related side effects.

Following diagnosis and surgery but prior to adjuvant therapy, 78.1% of breast cancer patients report experiencing high levels of stress (4). Stress is highest before chemotherapy and immediately after surgery (5), but tends to decline in the year following treatment (5,6). In contrast, symptoms of depression are higher during treatment compared to pre-treatment (7,8), peaking one year following treatment (8), particularly among those with pre-existing depressive symptoms (7), and can persist for up to a decade following diagnosis (8). Younger patients (18-39 years) report more severe depression than older patients, likely due to differing psychosocial challenges across life stages (9). Anxiety symptoms in breast cancer patients tend to peak at diagnosis (10) and during chemotherapy treatment (7), and while there is a progressive decrease, they can persist for up to six years post-diagnosis (10,11). Similarly to depression, patients with high pre-treatment trait anxiety experience higher state anxiety during treatment than those with lower baseline trait anxiety, indicating that individuals with a pre-existing anxious disposition are at higher risk for severe anxiety during treatment (10,12). Sleep disturbances affect 20%-70% of breast cancer patients (13) and can persist for up to a decade following treatment (14). Commonly reported issues include difficulty falling asleep, staying asleep, and early morning awakenings (14,15). During treatment, 60%-90% of women also report experiencing fatigue (16), with higher rates among those undergoing chemotherapy compared to radiation therapy (17). Cancer-related fatigue often emerges before treatment, worsens throughout the treatment period, and can persist for up to a decade following treatment (18). Although fatigue severity tends to decrease over time, it often does not return to baseline levels (19).

Mental health difficulties frequently co-occur in this population. For instance, depressive symptoms are commonly linked to increased anxiety, fatigue, and reduced quality of life (8,20,21). Similarly, anxiety is associated with heightened stress, sleep disturbances, fatigue, and lower quality of life (19,22,23). Sleep disturbances and fatigue are closely related and often co-occur with depression and anxiety, further contributing to diminished well-being (19,24). In addition to these mental health concerns, survivors frequently report long-term issues with cognitive functioning, sexual health (including fertility), body image, self-esteem, social relationships, and financial stability (25–28). These challenges are particularly pronounced among those who received chemotherapy as part of their cancer treatment (25,27).

Strong evidence supports the benefits of physical activity interventions for breast cancer both during treatment (29) and throughout survivorship (30). These interventions offer psychological advantages - including improved quality of life reductions in anxiety, depression, and fatigue (30–32) - as well as physiological benefits, such as enhanced cardiovascular health and reduced risk of cancer recurrence (31). Consequently, integrating physical activity into survivorship plans is widely recommended (31). However, there is evidence that while physical activity may reduce anxiety and improve quality of life, it does not consistently alleviate depressive symptoms in breast cancer survivors (33). Adherence to exercise programs is critical for achieving these benefits, yet can be influenced by various factors, including motivation, fatigue, pain, and mental health challenges (34).

Extensive research has examined pre- and post-treatment psychosocial factors such as stress, anxiety, fatigue, depression, sleep quality, as well as exercise in breast cancer survivors (5,8,10,14,18,33). However, few studies have explored the long-term interplay among these factors from a synergistic perspective, or directly compared these outcomes to women without a history of breast cancer. This study addresses this gap by examining the long-term effects of cancer treatment on multiple, interrelated psychosocial domains and evaluating how these patterns differ from those observed in a non-cancer comparison group of women. We hypothesized that breast cancer survivors would report high levels of perceived stress, anxiety,

depression, fatigue, and sleep disturbances compared to non-cancer controls. We also expected these psychosocial difficulties would be positively correlated, while greater engagement in physical activity would be associated with lower psychological distress. By examining these complex relationships, this study aims to inform the importance of comprehensive mental health assessments and the development of targeted interventions to enhance the long-term well-being and quality of life of breast cancer survivors.

2. Methods

2.1 Participants

We recruited female breast cancer survivors (BCS), aged 30 to 65, who were at least six-months post-chemotherapy treatment, and age-matched women without a history of breast cancer (healthy controls, HC). Participants were recruited through community outreach, public advertisements on social media, the community Integrated System of Participation in Research at the University of Ottawa, and the Cancer Foundation Maplesoft-Jones Centre. Exclusion criteria included: (1) a mental health diagnosis within the past 12 months, (2) a lifetime diagnosis of brain injury (e.g., concussion), neurodevelopmental (e.g., Attention-Deficit/Hyperactivity Disorder) or neurological disorder (e.g., stroke), (3) initiation of new mood-altering medications within the past 12 months, (4) current substance dependence or consuming cannabis more than 7 times per month, (5) lack of fluency in English, and (6) residence outside of Canada. Participants with these neurological disorders were excluded due to their potential impact on mental health outcomes. This study received full board review and approval from the University of Ottawa's Research Ethics Board (H-04-21-6706) and was conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

2.2 Procedure

Participants provided informed consent, then completed a comprehensive sociodemographic questionnaire assessing demographic (e.g., province of residence, education level, income) and health-related (e.g., mental health diagnoses, substance use, medications, and cancer treatment

details) factors. Participants then completed self-reported measures evaluating psychological and physical health indicators, including stress, depression, trait and state anxiety, fatigue, sleep quality, leisure-time exercise, and physical activity. This session took up to 60 minutes to complete online via Qualtrics, an online questionnaire distribution tool (RRID: SCR_016728). Participants completed the online questionnaires while connected via Zoom, a videoconferencing platform, with a member of the research team present to provide support.

2.3 Measures

The Perceived Stress Scale (PSS) is a reliable instrument for assessing perceived stress levels experienced in the past month (35). The self-reported questionnaire consists of 10 items rated on a 5-point Likert scale, with higher ratings indicating a higher level of perceived stress. The PSS demonstrates good reliability for perceived helplessness (McDonald's omega = .87) and acceptable reliability for self-efficacy (McDonald's omega = .73). Validity was assessed using confirmatory factor analysis and by assessing the relationship with another well validated measure assessing stress, anxiety, and depression (Depression Anxiety Stress Scale, DASS-21) which all demonstrated good validity in breast cancer patients (36). The PSS has been used numerous times with this patient population (4–6).

The State-Trait Anxiety Inventory (STAI) is a widely used self-reported measure that differentiates between situational (state) and general (trait) anxiety (37). It includes two 20-item scales: Form Y-1 or STAI-S (state anxiety), and Form Y-2 or STAI-T (trait anxiety), rated on a 4-point Likert scale, with scores above 39 indicating clinically significant levels of anxiety. Although no study has yet to formally assess the validity and reliability of this measure in breast cancer survivors, it has been widely used with this patient population (12,19,38,39).

The Centre for Epidemiologic Studies Depression Scale-Revised (CESD-R) is a 20-item self-report measure assessing depressive symptoms experienced within the past week, rated on a 5-point Likert scale (40). Higher scores indicate greater symptom severity. Scores below 16 indicate no clinical depression, whereas scores ≥16 indicate increasing levels of depressive severity, with thresholds for subclinical, possible, probable, and major depressive episodes based on the

presence and frequency of anhedonia, dysphoria, and other symptoms. The psychometric properties of the CESD-R have only been measured in a sample of Chinese patients with cancer which revealed good internal consistency (Cronbach's alpha, α = .82 – .88) and acceptable construct validity when the CESD-R was compared with the depression module of the Patient Health Questionnaire (*rho* = .73) (41). The CESD-R has been previously used with this patient population (8,18).

The Fatigue Severity Scale (FSS) is a 9-item self-report measure assessing fatigue over the past 30 days, rated on a 7-point Likert scale with higher scores indicating a greater level of fatigue (42). While no specific clinical cutoff scores have been established for the FSS, the scale has excellent internal consistency in cancer patients (α = .96) (43).

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item self-report measure assessing sleep quality over the past month (44). Items form seven subscales, or components, which are summed to produce a global score, with scores >5 reflecting poor sleep. The PSQI has acceptable internal consistency (α = .79) and convergent validity (*r* = .72 to .81) which was measured by assessing the relationship between the PSQI and four other sleep scales in cancer populations (45), and has been frequently used with breast cancer patients (14,15,24).

The Leisure Time Exercise Questionnaire (LTEQ) assesses weekly leisure-time physical activity (46). It includes two items: the first items measure frequency of mild, moderate, and strenuous exercise (>15 minutes per session), and the second assesses the frequency of heart rate elevation during these activities, using a 3-point Likert scale. Higher scores reflect greater activity, with <14 units indicating sedentary behavior, 14-23 moderately active, and >24 units active.

The International Physical Activity Questionnaire (IPAQ) short form is a 7-item self-report measure of physical activity and sedentary behavior over the past week (47). It assesses time spent on vigorous and moderate activities, walking (>10 minutes per session), and sitting. A composite Metabolic Equivalent Task (MET) score is calculated, with a higher score indicating greater physical activity. Activity levels are classified as: low (not meeting criteria for moderate or

high activity), moderate (>3 days/week of vigorous activity for >30 min/day, >5 days/week of moderate activity and/or walking for >30 min/day, or >5 days/week of any activity for >600 MET-min/week), or high (>3 days/week of vigorous activity for >1500 MET-min/week, or 7 days/week of any activity for >3000 MET-min/week).

2.4 Statistical Analysis

Questionnaire data were collected using Qualtrics (RRID: SCR_016728) and scored using a script in R-Studio (RRID: SCR_001905). Statistical analyses were performed in SPSS 28 (RRID: SCR_002865). For this between-subjects design, independent sample t-tests evaluated group differences in stress, fatigue, anxiety, depression, sleep quality, and physical activity. To evaluate the interrelationships among key mental health constructs (stress, depression, anxiety, fatigue, sleep quality), Pearson correlation (*r*) analyses were conducted to assess the strength and direction of their associations. Statistical significance was set at $p < .05$, with Bonferroni corrections applied to adjust the alpha level for multiple comparisons. We conducted eight multiple regression analyses, one for each outcome variable—stress, trait anxiety, state anxiety, depression, sleep quality, fatigue, exercise, and physical activity. Each model included all demographic and health-related predictors: age, education, income, and menopausal status (for both groups), as well as time since treatment and current hormonal therapy (for breast cancer survivors only). Figures were created using GraphPad Prism (RRID: SCR_002798).

3. Results

3.1 Participant Characteristics

A total of 109 participants completed the demographic, health, and mental health questionnaires. Of these, 16 were excluded (*n* = 11 BCS, *n* = 5 HC) based on the exclusion criteria. Among the 93 eligible participants (*n* = 49 BCS; *n* = 44 HC), the majority identified as White (BCS: 93.9%; HC: 81.8%), held a bachelor's degree (BCS: 46.9%; HC: 38.6%), and reported a family income between $100,000 and $200,000 (BCS: 46.9%; HC: 38.6%). Substance use was reported by 49.0% of breast cancer survivors and 61.4% of controls, with alcohol being

the most used substance, and occasional cannabis use of no more than 7x per month. A lifetime history of mental health diagnoses (e.g., anxiety, depressive, eating, and post-traumatic stress disorders), was reported by 12.2% of breast cancer survivors and 18.2% of controls, with no participants reporting symptoms in the past 6 months. Long-term use of mood-altering medication (over one year) was reported by 14.3% of breast cancer survivors, compared to 11.4% of controls. Finally, 81.6% of breast cancer survivors and 54.5% of controls were post-menopausal (Table 1). See Table 2 for cancer and treatment-related information.

Table 1. *Participant demographics.* Abbreviations: BCS, breast cancer survivors; HC, healthy controls; M, mean; n, sample size; SD, standard deviation; %, percentage.

	BCS (*n* = 49)	HC (*n* = 44)
	M (*SD*) or % (*n*)	M (*SD*) or % (*n*)
Age	50.71 (8.58)	50.16 (10.71)
Province of residence		
Alberta	0.00% (0)	4.50% (2)
British Columbia	4.10% (2)	9.10% (4)
Manitoba	8.20% (4)	0.00% (0)
New Brunswick	2.00% (1)	0.00% (0)
Nova Scotia	4.10% (2)	0.00% (0)
Northwest Territories	4.10% (2)	0.00% (0)
Ontario	59.20% (29)	68.20% (30)
Prince Edward Island	2.00% (1)	2.30% (1)
Quebec	12.20% (6)	11.40% (5)
Saskatchewan	4.10% (2)	2.30% (1)
Yukon	0.00% (0)	2.30% (1)
Race		
White	94.00% (46)	81.80% (36)
Black	0.00% (0)	2.30% (1)
Greek	2.00% (1)	0.00% (0)
East Asian	0.00% (0)	2.30% (1)
South Asian/East Indian	2.00% (1)	2.30% (1)
Indigenous	0.00% (0)	2.30% (1)
Latin American	0.00% (0)	2.30% (1)
Person of mixed origin	0.00% (0)	2.30% (1)
Turkish	2.00% (1)	0.00% (0)
West Asian, North African, Arab	0.00% (0)	2.30% (1)
I prefer not to answer	0.00% (0)	2.30% (1)
Completed Education Level		
High school diploma	6.10% (3)	2.30% (1)
College degree	24.50% (12)	20.50% (9)
Bachelor's degree	46.90% (23)	38.60% (17)
Master's degree	16.30% (8)	27.30% (12)
Doctorate degree	2.00% (1)	6.80% (3)
Other	4.00% (2)	4.60% (2)
Income		
< $30 000	0.00% (0)	6.80% (3)
$30 000 - $50 000	2.00% (1)	9.10% (4)
$50 000 - $100 000	24.50% (12)	22.70% (10)
$100 000 - $200 000	46.90% (23)	39.00% (17)
> $200 000	20.40% (10)	11.00% (5)
I prefer not to answer	6.10% (3)	11.40% (5)
Current Substance Use (Yes, %)	49.00% (24)	61.40% (27)
Drug-Frequency		
Daily	22.40% (11)	27.30% (12)
2-3 times per week	8.20% (4)	13.60% (6)
Once per week	2.00% (1)	9.10% (4)
Once per month	24.50% (12)	22.70% (10)
Not applicable	42.90% (21)	27.30% (12)
Mental Health Diagnosis (Yes, %)	12.20% (6)	18.20% (8)
Medications (Yes, %)	81.60% (40)	52.30% (23)
Mood Altering Medications (Yes, %)	14.30% (7)	11.40% (5)
Menopausal		
Pre-menopausal	18.40% (9)	45.50% (20)
Post-menopausal	81.60% (40)	54.50% (24)

Table 2. *Breast cancer diagnosis and treatment details.*

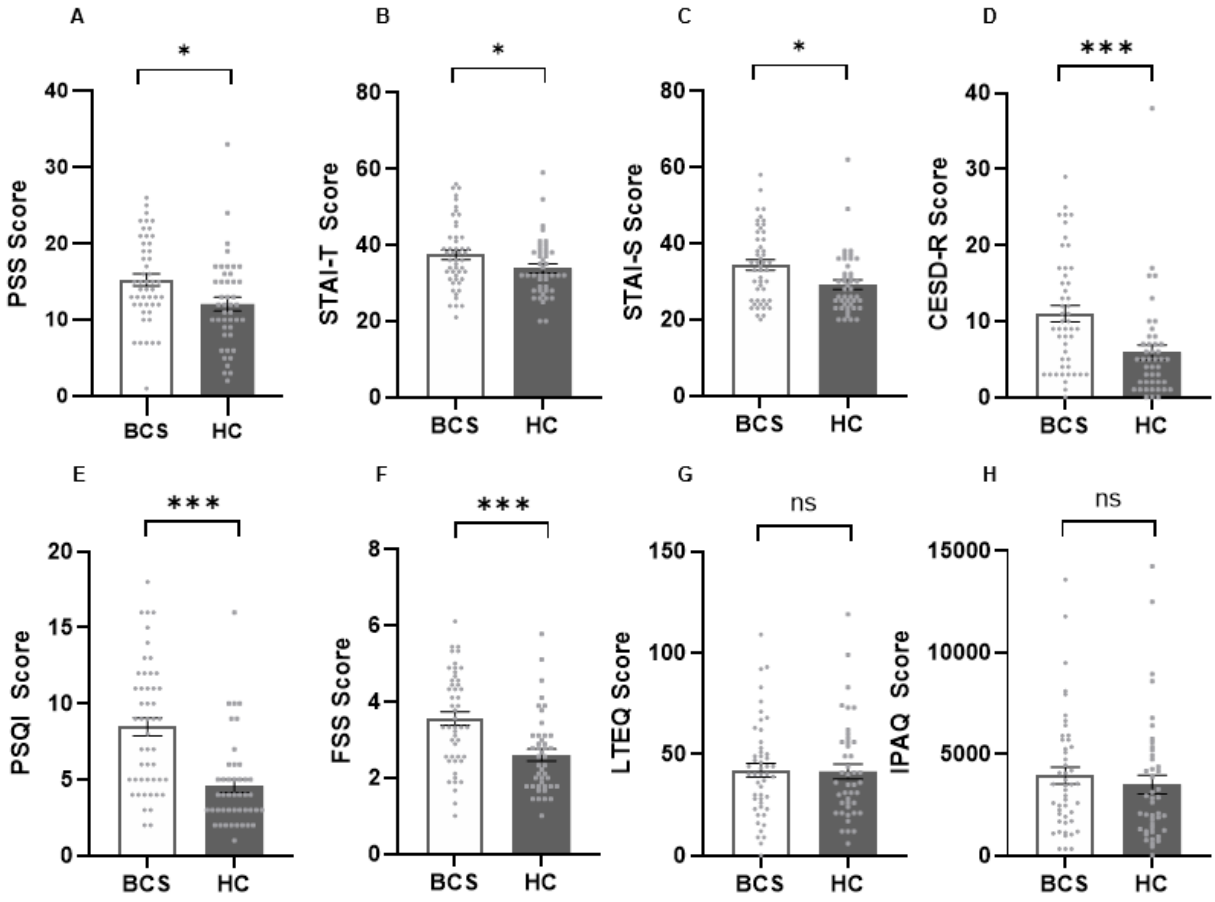
	Percentage (sample size)
Time since Diagnosis	
1-2 years ago	16.00% (8)
2-5 years ago	51.00% (25)
5-10 years ago	20.40% (10)
>10 years ago	12.20% (6)
Cancer Stage at Diagnosis	
Stage 0	2.00% (1)
Stage 1	18.00% (9)
Stage 2	42.90% (21)
Stage 3	32.70% (16)
Unknown	4.10% (2)
Treatment End	
6-12 months ago	14.30% (7)
1-2 years ago	28.60% (14)
2-5 years ago	28.60% (14)
5-10 years ago	20.40% (10)
>10 years ago	8.20% (4)
Current Hormone Therapy	
Yes	51.00% (25)
No	6.10% (3)
Not applicable	42.90% (21)
Treatment	
Chemotherapy	100.00% (49)
Hormonal Therapy	57.10% (28)
Radiation Therapy	77.60% (38)
Surgery	100.00% (49)
Immunotherapy	4.10% (2)
Targeted Therapy	18.40% (9)

3.2 Group Differences Between Stress, Anxiety, Depression, Fatigue, Sleep Quality, and Physical Activity

Breast cancer survivors reported higher levels of perceived stress compared to non-cancer controls [$t(91) = 2.67$, $p = .004$, Cohen's $d = 0.55$] (Figure 1A), where breast cancer survivors reported moderate levels of perceived stress whereas healthy controls reported low levels according to PSS cut-off scores. Despite breast cancer survivors reporting sub-clinical levels of anxiety (STAI > 39), they reported significantly more symptoms than controls [STAI-T: $t(91) = 2.08$, $p = .02$, $d = .43$; STAI-S: $t(91) = 2.76$, $p = .003$, $d = .57$] (Figure 1B, C). Similarly, symptoms of depression were also higher among breast cancer survivors [$t(90.95) = 3.52$, $p < .001$, $d = .72$], although, these levels were within the non-clinical range (CESD-R <16) (Figure 1D). Sleep quality also significantly differed between groups [$t(86.01) = 5.23$, $p < .001$, $d = 1.06$] with breast cancer

survivors categorized as poor sleepers (PSQI ≥ 5) and healthy controls classified as good sleepers (PSQI < 5) (Figure 1E). Fatigue also differed among groups [$t(91) = 4.02$, $p < .001$, $d = .83$] with breast cancer survivors reporting heightened levels of fatigue compared to controls (Figure 1F). After applying Bonferroni correction (adjusted $\alpha = .006$), group differences in perceived stress, state anxiety, depression, fatigue, and sleep disturbances remained statistically significant. While breast cancer survivors engaged in less leisure-time exercise, they reported a higher overall level of physical activity compared to controls; however, neither difference was statistically significant [leisure-time exercise: $t(91) = -.93$, $p = .17$, $d = -.19$ (Figure 1G); MET activity: $t(91) = 1.12$, $p = .13$, $d = .23$] (Figure 1H).

Figure 1. *Mean scores on the self-report questionnaires. (A) Perceived stress, (B) trait anxiety (did not survive correction for multiple comparisons), (C) state anxiety, (D) depression, (E) sleep quality, (F) fatigue, (G) leisure time exercise, and (H) physical activity among breast cancer survivors (white bars) and controls (grey bars).* Individual data points for each group are presented in light grey. Error bars represent the standard error of the mean. Abbreviations: BCS, breast cancer survivor; CESD-R, center for epidemiologic studies depression scale-revised; FSS, fatigue severity scale; HC, healthy control; IPAQ, international physical activity questionnaire; LTEQ, leisure time exercise questionnaire; PSQI, Pittsburgh sleep quality inventory; PSS, perceived stress scale; STAI-S, state-trait anxiety inventory – state scale; and STAI-T, state-trait anxiety inventory – trait scale. * denotes $p < .05$, *** denotes $p < .001$, ns denotes no significant difference ($p > .05$).



Based on Cohen's guidelines, the effect sizes indicated a negligible difference between breast cancer survivors and healthy controls in leisure time exercise (48). Small effects were observed overall physical activity and moderate effect sizes were found for perceived stress, depression, and state anxiety. The largest differences emerged in fatigue and sleep quality, which showed large effect sizes.

Reliability analyses demonstrated excellent internal consistency for the PSS (α = .90), STAI-S (α = .93), STAI-T (α = .91), and FSS (α = .90). The CESD-R (α = .87) demonstrated good internal consistency, while the PSQI (α = .78) showed acceptable internal consistency among participants in this study. Given that the LTEQ and IPAQ are open-ended questions, and not a Likert scale, no reliability analyses were conducted for these measures.

3.3 Correlations Between Stress, Anxiety, Depression, Fatigue, Sleep Disturbances, and Physical Activity

Pearson correlation analyses were conducted to examine relationships among the various constructs. In both groups, significant positive correlations were observed between stress and depression, state anxiety, trait anxiety, and fatigue (*p*'s < .05). Similarly, state anxiety was positively correlated with stress, depression, trait anxiety, and fatigue (*p*'s < .05), while trait anxiety showed significant correlations with depression and fatigue (*p*'s < .05). Depression was also positively correlated with both fatigue and sleep quality (*p*'s < .05), and physical activity was significantly correlated with leisure time exercise (*p*'s < .05). Notably, sleep quality was significantly correlated with state and trait anxiety, and stress, but only in controls (*p*'s < .05). Full correlation coefficients are presented in Table 3.

Table 3. *Pearson correlation matrix between stress, depression, anxiety, fatigue, sleep quality, and physical activity for breast cancer survivors and healthy controls.* Abbreviations: BCS, breast cancer survivor; CESD-R, center for epidemiologic studies depression scale-revised; FSS, fatigue severity scale; HC, healthy control; IPAQ, international physical activity questionnaire; LTEQ, leisure time exercise questionnaire; PSQI, Pittsburgh sleep quality inventory; PSS, perceived stress scale; STAI-S, state-trait anxiety inventory – state scale; and STAI-T, state-trait anxiety inventory – trait scale. * denotes *p* < .05.

Group	Measures	PSS	CESD	STAI-S	STAI-T	FSS	PSQI	LTEQ	IPAQ
BCS	PSS	1							
	CESD	.67*	1						
	STAI-S	.81*	.65*	1					
	STAI-T	.78*	.59*	.81*	1				
	FSS	.53*	.47*	.36*	.41*	1			
	PSQI	.21	.43*	.14	.07	.08	1		
	LTEQ	.04	.026	.01	.07	-.10	-.09	1	
	IPAQ	-.06	-.03	-.10	-.05	-.15	-.13	.65*	1
HC	PSS	1							
	CESD	.69*	1						
	STAI-S	.83*	.77*	1					
	STAI-T	.85*	.69*	.81*	1				
	FSS	.52*	.62*	.52*	.56*	1			
	PSQI	.38*	.53*	.31*	.27*	.15	1		
	LTEQ	.03	.04	.12	.11	.09	-.14	1	
	IPAQ	-.10	-.02	.01	-.21	-.06	-.12	.43*	1

3.4 Exploratory Multiple Regression Analyses

As a set, the variables age, education, income, menopausal status, time since treatment, and current hormonal therapy collectively predicted stress and physical activity in breast cancer survivors (p = .004 and p = .03, respectively), but not in healthy controls (*p* = .06 and *p* = .07, respectively). In contrast, these variables predicted depression in healthy controls (*p* = .02), but not in breast cancer survivors (*p* = .45). All variables predicted state anxiety in breast cancer survivors (*p* = .02) and healthy controls (*p* = .01). However, none of the variables collectively predicted trait anxiety, fatigue, sleep quality, or leisure exercise in either group (*p*'s > .05). Examining individual predictors, multiple regression analyses in breast cancer survivors revealed that age significantly predicted stress, state anxiety, while income predicted both stress and physical activity (*p*'s < .05). In the control group, education predicted depression and state anxiety, while both income and menopausal status were significant predictors of depression (*p*'s < .05). Complete regression statistics can be found in Table 4.

Table 4. *Regression between age, income, education, menopausal status, time since treatment and psychological and physical activity outcomes.* Abbreviations: BCS, breast cancer survivors; HC, healthy controls; B, unstandardized coefficients; Std Error, unstandardized standard error; β, standardized coefficient beta.

Outcome	Group	Variables	B	Std. Error	t	β	p
Stress	BCS	Age	-.35	.11	-3.55	-.54	.001
		Income	3.72	1.65	2.25	.29	.03
Depression	HC	Income	.95	.45	2.09	.32	.03
		Education	4.41	2.01	2.18	.31	.04
		Menopausal status	-7.74	3.53	-2.19	-.58	.03
State Anxiety	BCS	Age	-.55	.18	-3.01	-.48	.004
	HC	Education	1.39	.55	2.51	.37	.01
Physical Activity	BCS	Income	28.75	8.28	3.47	.48	.001

4. Discussion

This study provides a comprehensive examination of the long-term psychological impacts of breast cancer treatment, identifying that survivors experience significantly elevated levels of

stress, anxiety, depression, fatigue, and sleep disturbances compared to women without a history of cancer. These results are consistent with prior research identifying elevated levels of stress (6), anxiety (10,11), depression (8), sleep disturbances (15), and fatigue (18,19) in breast cancer survivors, some persisting up to a decade post-diagnosis (8,10,11,14,18). Our findings contribute to the literature by directly comparing the psychological functioning of breast cancer survivors to that of non-cancer controls, offering a clearer understanding of the unique challenges associated with cancer survivorship.

Although breast cancer survivors reported greater symptoms of depression and anxiety compared to controls, both groups scored within the subclinical range based on established cutoffs. Given that the measures used were intended for screening rather than diagnostic evaluation, a more comprehensive clinical assessment is necessary to determine whether survivors meet criteria for mood or anxiety disorders. Subclinical mental health symptoms, while often overlooked, can still impair quality of life, and may go untreated without proper screening and intervention. Overall, these findings point to an increased psychological vulnerability among breast cancer survivors, and emphasize the importance of proactive, ongoing monitoring. Preventive strategies and tailored support services may reduce the progression of subclinical symptoms into clinically significant mental health conditions.

Higher perceived stress was significantly correlated with increased depression, anxiety, and fatigue in both breast cancer survivors and non-cancer controls, consistent with prior reports (49). Interestingly, while perceived stress was associated with greater sleep disturbances in controls, this relationship was not observed among breast cancer survivors. This finding contrasts with prior research in U.S. breast cancer survivors up to 5 years post-diagnosis, which reported a positive association between stress and sleep disturbances (50). Similarly, higher anxiety levels were positively correlated with stress, depression, and fatigue in both groups, consistent with earlier reports (22,49). However, anxiety was linked to sleep disturbances only in the control group. This diverges from an earlier study that identified an association between anxiety and poor sleep quality in breast cancer survivors within 1 - 5 years post-treatment, although different

measures were used (23). Depression was associated with elevated stress, anxiety, fatigue, and sleep disturbances across both groups, consistent with prior reports (18,22,23). These findings suggest a synergistic relationship, where difficulties in one domain may be associated with increased in others.

The role of physical activity in cancer survivorship is well-documented, with most studies focusing on intervention-based approaches (30,31). Observationally, we found no significant difference in self-reported physical activity levels among breast cancer survivors compared to non-cancer controls, which contrasts with prior reports of reduced physical activity among breast cancer survivors (51). Further, physical activity did not significantly correlate with perceived stress, depression, anxiety, fatigue, or sleep quality in either group. Despite widespread recommendations for physical activity as part of cancer survivorship care, evidence for its psychological benefits is mixed. Our results align with studies reporting no significant impact of physical activity interventions on depression in breast cancer survivors (see review (33)). However, they contrast with research showing improvements in anxiety, fatigue, and depression, and sleep quality following physical activity interventions in survivors 2 -10 years post-treatment (31,32,52). These inconsistencies may reflect a range of factors, including time since diagnosis or treatment, age, treatment regime, types and intensities of physical activity, and assessment methods. Such variability suggests that the therapeutic benefits of physical activity may depend on specific contextual factors, and that a threshold of activity (e.g., duration, intensity, type) may be required to achieve robust benefits in cancer survivorship.

An exploratory analysis was conducted to examine the relationship between demographic and health-related variables (age, income, education, menopausal status, time since treatment, and current hormonal therapy) and mental health outcomes (stress, anxiety, depression, fatigue, and sleep disturbances) among breast cancer survivors and healthy controls. Among breast cancer survivors, age significantly predicted perceived stress and state anxiety, while in non-cancer controls, age was a predictor only of depression. Income was associated with levels of stress and physical activity among breast cancer survivors, but predicted only depression in non-

cancer controls. However, among non-cancer controls, education was a predictor of depression and state anxiety while menopausal status was associated with depression. These findings are consistent with previous research indicating that age is a predictor for mental health concerns, particularly in younger cancer survivors (53), and that younger survivors with a lower income are at a heightened risk for distress and diminished quality of life (54,55). Notably, time since diagnosis was not significantly associated with anxiety or depression in our sample, supporting earlier findings (22). While some survivors experience improvements in mental health over time (56), our results suggest that many continue to struggle with psychological distress long after treatment completion. These enduring challenges can significantly impact survivors' quality of life, including their ability to return to work (8,10,11,14). However, our results contrast with prior studies that reported associations between menopausal status and income with sleep disturbances (14,23), and between education level and psychological distress (55) in breast cancer survivors. Overall, mental health outcomes in breast cancer survivors are shaped by various demographic and health-related factors, with age emerging as the most significant predictor. However, some of these findings diverge from previous research, underscoring the complexity and variability of mental health experiences among cancer survivors.

This cross-sectional study was conducted online which allowed for the inclusion of a geographically diverse sample across Canada, reduced transportation burden, minimized risk for immunocompromised individuals, and was cost-effective. However, this recruitment method also has limitations. It relies heavily on access to social media, which tends to skew towards younger individuals and certain ethnic groups (57). As a result, the participant sample was predominantly white and well-educated, limiting the generalizability of findings to the broader population of breast cancer survivors. Future studies should prioritize strategies to recruit more diverse and representative samples. Considering the limitations of self-report measures, future studies should incorporate clinical interviews alongside standardized questionnaires to gain a more comprehensive understanding of the mental health challenges, including symptom frequency, intensity, and duration. Additionally, objective measures (e.g., accelerometers or activity trackers) should be used to assess physical activity levels more accurately.

Given the heterogeneity of cancer treatments and their dose-dependent effects – particularly chemotherapy (58) – future research should collect detailed treatment data and adopt longitudinal designs to better understand the long-term impacts of cancer and its treatment. Finally, discrepancies across studies may be influenced by various factors, including menopausal status, age at diagnosis, cancer stage, time since treatment, treatment type and dosage, pre-existing psychological conditions, demographic variables, exercise regimes, and outcome measures. Sufficiently powered future studies should account for these covariates on mental health outcomes among cancer survivors.

5. Conclusion

This study contributes to the growing body of evidence highlighting the long-term psychological effects of cancer treatment in breast cancer survivors. Our findings demonstrate that many breast cancer survivors continue to experience substantial mental health challenges – including stress, anxiety, depression, fatigue, and sleep disturbances – long after completing primary cancer treatment. These issues are not isolated, but interconnected, collectively influencing survivors' overall well-being. Given these persistent challenges, it is essential to integrate continuous, comprehensive assessments into cancer survivorship plans, considering a wide range of demographic, clinical, and psychosocial factors that may affect mental health functioning. This approach will facilitate the identification of both emerging and ongoing psychological concerns. Such assessments can also inform the development of holistic interventions that address the interconnected nature of survivors' mental health needs. Future research should focus on identifying the underlying factors contributing to these persistent mental health challenges, and develop targeted, evidence-based strategies to minimize their impact and improve the quality of life for breast cancer survivors.

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CHAPTER 4

Limitations of Standard Memory Assessment in Breast Cancer Survivors

Meenakshie Bradley-Garcia[1], Annick F. N. Tanguay[1], Gabriela Haddad[1], Adelaide Jensen[1], Melanie J. Sekeres[1]

[1]School of Psychology, University of Ottawa, Ottawa, Ontario, Canada

Authors note

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Abstract

Breast cancer is the most commonly diagnosed cancer in women worldwide, and treatments like chemotherapy are often linked to post-treatment cognitive impairments, including memory deficits. Standardized episodic memory tests may fail to capture the nuanced, real-world aspects of memory, potentially underestimating impairments in cancer survivors. This study seeks to investigate the impact of cancer treatment on episodic memory in breast cancer survivors (BCS) by comparing standard cognitive measures with ecologically valid measures of naturalistic memory, which may capture the subtle memory impairments. BCS at least 6 months post-treatment (n = 45) and non-cancer control (NC; n = 43), aged 30 to 65, completed two cognitive tasks to assess episodic memory (Taler Stories and Verbal Paired Associates, VPA) and two questionnaires to assess perceived cognitive workload (National Aeronautics and Space Administration Task Load Index) and perceived episodic and semantic memory abilities (Survey of Autobiographical Memory). BCS recalled fewer verbatim and gist details for the Taler Stories than NC, with impairments in gist memory persisting during delayed recall. However, no memory deficits were evident on the VPA task in BCS compared to NC. BCS reported greater cognitive effort during the story recall tasks, but no group differences emerged for the VPA task. BCS also self-reported heightened subjective difficulties with episodic and semantic memory compared to NC, which was consistent with poorer performance on the Taler Stories. Impaired performance on complex naturalistic memory, despite similar VPA memory task performance, suggests that standard assessments may not fully capture everyday memory challenges faced by BCS.

Keywords: breast cancer; cancer treatment; episodic memory; ecological validity; chemofog

1. Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide, accounting for one in every four diagnoses in women (1). Although cancer treatments have substantially improved survival rates (2), growing evidence highlights treatment-related cognitive side effects, particularly with chemotherapy (3). Colloquially known as “chemobrain”, chemotherapy-related difficulties in memory, executive function, and processing speed (4) commonly emerge during or after treatment and may persist for years (5,6). These cognitive changes can hinder interpersonal, occupational, and everyday functioning, and ultimately reduce quality of life (7).

Memory impairment, including episodic memory, is frequently reported by breast cancer survivors (BCS) (8,9). Episodic memory involves the vivid recollection of personal events, including temporal, contextual, and perceptual details (e.g., recalling the last Olympic gold medal hockey game) (10). While rich in detail, episodic memories can co-exist with gist-like versions that convey general event content but lack specific, vivid features (11,12). Both fine-grained episodic details and more coarsely-grained gist-like details depend on the hippocampus, engaging posterior and anterior regions respectively (13–15). Over time, as a memory becomes less episodically-detailed and more schematized (generalized representation of a class of event; e.g., memory of a typical hockey game) (16,17), its retrieval may become increasingly supported by the medial prefrontal cortex (mPFC) and less dependent upon detailed hippocampal representations (11,18–20). In contrast, semantic memory refers to general knowledge and facts (e.g., knowing each team has 6 players on the ice), and is not linked to a specific event (10). Due to episodic memory’s reliance on the hippocampus for encoding and detailed retrieval, episodic memory is especially vulnerable to conditions that affect hippocampal integrity (21). Consequently, individuals with medial temporal lobe damage often show impaired recollection of episodically-specific event details while relying on more generalized, mPFC-dependent schematic representations and semantic knowledge to support memory retrieval (12).

Numerous classes of chemotherapeutic drugs are neurotoxic to the hippocampus, causing structural (e.g., volume reduction, deformation, neurogenesis) (8,22–25) and functional (e.g.,

altered activity and connectivity) (24,26,27) hippocampal disruptions, offering potential mechanisms underlying chemotherapy-related episodic memory deficits (28). Along the hippocampal long-axis, reduced posterior hippocampal volume predicted impoverished episodic autobiographical memory in breast cancer survivors (22), suggesting that episodically-detailed narrative memory is particularly vulnerable to impairment post-treatment, while more schematic representations may be less affected.

Conventional memory assessments used to assess episodic memory, including list learning and verbal paired associate tasks, though reliable, often lack ecological validity and may not reflect real-world cognitive functioning (29). For instance, list-learning tasks assess immediate recall but lack everyday demands such as remembering conversations or personal events. BCS often show poorer performance on early list learning trials, suggesting initial encoding challenges that improve with repetition and familiarity (30–32). However, some show delayed recall impairments despite intact immediate recall and recognition, suggesting deficits in retrieval rather than encoding deficits (6,32). Other studies report no differences between BCS and controls (33,34), highlighting the complexity of cognitive impairments and the need for assessments that better characterize memory processing differences with a higher degree of sensitivity.

Unlike the arbitrary word pairs used in verbal paired associates tasks, narrative memory assessments engage more complex mnemonic processes including schematic and semantic representations, and require the construction and maintenance of complex temporal and contextual relational structures within an event (35). Consequently, narrative memory tasks offer greater ecological validity and are more sensitive to detecting subtle memory disruptions across multiple mnemonic domains. Naturalistic memory tasks like narrative recall, better mimic real-life memory experiences and can evaluate precise verbatim recollection, gist-based recall, and memory distortions during recollection of complex events (36). This is meaningful as verbatim memory typically declines with age, while gist memory remains more stable and less affected by hippocampal damage (36,37). Supporting this, a study using the Wechsler Memory Scale – Logical Memory (WMS – LM) story recall task found that BCS who were 5-15 years post-

treatment initially recalled fewer narrative details than non-cancer controls (NC), although this difference resolved eight months following baseline (30). By using unit-based scoring of narrative recollection, including verbatim, gist, and distortion sub-types, we can potentially detect more subtle memory impairments that may not be captured by dichotomous scoring (i.e., correct or incorrect) (38) used in standardized memory assessments like verbal paired associates and the original scoring for the WMS-LM, leading to an underestimate of cognitive impairment.

Compounding this challenge, BCS often experience subjective cognitive decline post-chemotherapy (9), even in cases which fail to show impairments using objective measures (39). A potential variable contributing to this discrepancy is perceived cognitive workload, or the mental effort required to complete a task (41), which is influenced by cognitive reserve, task complexity, and neural efficiency (42). In addition to the hippocampal neurotoxicity discussed above, chemotherapy treatment leads to broader structural and functional changes throughout the brain (e.g., prefrontal hyperactivation, decreased grey and white matter integrity, and alterations in the default mode network) (43–45), which may contribute to inefficient network processing during cognitive tasks. The mismatch between objective and subjective complaints by cancer survivors may reflect the need to engage energy-intensive neural compensatory mechanisms in order to effortfully perform at control levels (46,47).

This study examined whether an ecologically valid measure of narrative event memory could identify subtle memory deficits that may not be captured by a standard episodic memory assessment. We hypothesized that BCS would recall fewer episodically rich (i.e., verbatim) details during recall of the Taler Stories relative to NC. Additionally, we expected BCS to exhibit more difficulty recalling word pairs during the first trial of the Verbal Paired Associates (VPA) task, with improvements across trials. Memory performance was predicted to be associated with higher cognitive effort reported by BCS.

2. Methods

2.1 Participants

We recruited female BCS, aged 30 to 65, who were >6 months post-treatment, and age-matched NC. Recruitment was conducted through community outreach, social media advertisements, the University of Ottawa's Integrated System of Participation in Research community pool, and the Cancer Foundation Maplesoft-Jones Centre at the Ottawa Regional Cancer Foundation. Exclusion criteria included: a mental health diagnosis and/or initiating mood-altering medications within <12 months, a lifetime diagnosis of a neurodevelopmental or neurological disorder, current substance dependence or cannabis use >7 times/month, non-fluency in English, residence outside of Canada, and a Montreal Cognitive Assessment (MoCA) score ≤21 (48). Of the ninety-three eligible participants, two withdrew (BCS, *n* = 2) and three were excluded due to audio recording failures (BCS, *n* = 2; NC, *n* = 1), resulting in a sample of 88 participants (BCS, *n* = 45; NC, *n* = 43; Tables 1 and 2). The study was approved by the University of Ottawa's Research Ethics Board (H-04-21-6706) and adhered to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Table 1. *Participant Demographics.* Abbreviations: BCS, breast cancer survivors; NC, non-cancer controls; M, mean; *n*, sample size; SD, standard deviation; %, percentage.

	BCS (*n* = 45)	NC (*n* = 43)
	M (*SD*) or % (*n*)	M (*SD*) or % (*n*)
Age	51.22 (8.73)	49.88 (10.67)
Race		
White	95.6 % (43)	81.4 % (35)
Black	0.0 % (0)	2.3 % (1)
East Asian	0.0 % (0)	2.3 % (1)
South Asian/East Indian	2.2 % (1)	2.3 % (1)
Indigenous	0.0 % (0)	2.3 % (1)
Latin American	0.0 % (0)	2.3 % (1)
Person of mixed origin	0.0 % (0)	2.3 % (1)
Turkish	2.2 % (1)	0.0 % (0)
West Asian, North African, Arab	0.0 % (0)	2.3 % (1)
Prefer not to answer	0.0 % (0)	2.3 % (1)
Province of Residence		
Alberta	0.0 % (0)	4.7 % (2)
British Columbia	4.4 % (2)	9.3 % (4)
Manitoba	8.9 % (4)	0.0 % (0)
New Brunswick	2.2 % (1)	0.0 % (0)
Nova Scotia	4.4 % (2)	0.0 % (0)
Northwest Territories	4.4 % (2)	0.0 % (0)
Ontario	55.6 % (25)	69.8 % (30)
Prince Edward Island	2.2 % (1)	0.0 % (0)
Quebec	13.3 % (6)	11.6 % (5)
Saskatchewan	4.4 % (2)	2.3 % (1)
Yukon	0.0% (0)	2.3 % (1)
Completed Education Level		
High school diploma	6.7 % (3)	2.3 % (1)
College degree	24.4 % (11)	18.6 % (8)
Bachelor's degree	44.4 % (20)	39.5 % (17)
Master's degree	17.8 % (8)	27.9 % (12)
Doctorate degree	2.2 % (1)	7.0 % (3)
Other	4.4 % (2)	4.6 % (2)
Income		
< $30 000	0.0 % (0)	7.0 % (3)
$30 000 - $50 000	2.2 % (1)	9.3 % (4)
$50 000 - $100 000	24.4 % (11)	20.9 % (9)
$100 000 - $200 000	46.7 % (21)	39.5 % (17)
> $200 000	20.0 % (9)	11.6 % (5)
I prefer not to answer	6.7 % (3)	11.6 % (5)
Current Substance Use	46.7 % (21)	60.5 % (26)
Drug-Frequency		
Daily	20.0 % (9)	27.9 % (12)
2-3 times per week	8.9 % (4)	11.6 % (5)
Once per week	2.2 % (1)	9.3 % (4)
Once per month	22.2 % (10)	23.3 % (10)
Not applicable	46.7 % (21)	27.9 % (12)
Mental Health Diagnosis (Lifetime)	13.3 % (6)	16.3 % (7)
Mental Health Symptoms (Past 12 months)	0.0 % (0)	4.7 % (2)
Mental Health Symptoms (Past 6 months)	0.0 % (0)	0.0 % (0)
Medications	82.2 % (37)	51.2 % (22)
Mood Altering Medications	13.3 % (6)	9.3 % (4)
Menopausal Status	82.2 % (37)	53.5 % (23)

Table 2. *Breast Cancer Diagnosis and Treatment Details.*

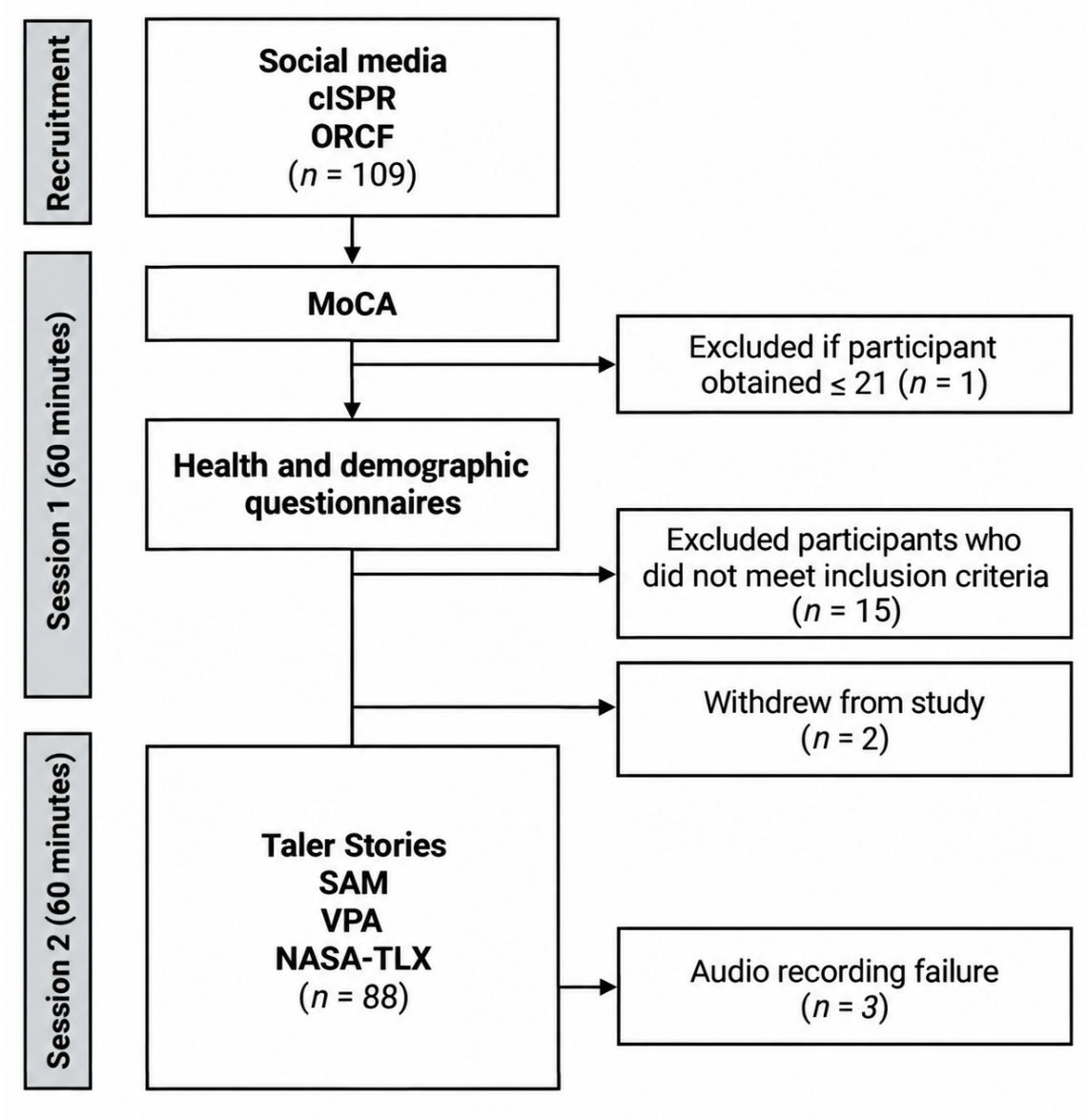
	Percentage (sample size)
Time Since Diagnosis	
1-2 years ago	17.8 % (8)
2-5 years ago	48.9 % (22)
5-10 years ago	20.0 % (9)
>10 years ago	13.3 % (6)
Cancer Stage at Diagnosis	
Stage 0	2.2 % (1)
Stage 1	15.6 % (7)
Stage 2	44.4 % (20)
Stage 3	33.3 % (15)
Unknown	4.4 % (2)
Treatment End	
6-12 months ago	15.6 % (7)
1-2 years ago	28.9 % (13)
2-5 years ago	26.7 % (12)
5-10 years ago	20.0 % (9)
>10 years ago	8.9 % (4)
Treatment	
Chemotherapy	100.0 % (45)
Hormonal Therapy	60.0 % (27)
Radiation Therapy	80.0 % (36)
Surgery	100.0 % (45)
Immunotherapy	4.4 % (2)
Targeted Therapy	17.8 % (8)
Current Hormone Therapy	
Yes	53.3 % (24)
No	6.7 % (3)
Not applicable	40.0 % (18)

2.2 Procedure

This study involved two online sessions, each lasting up to 60 minutes (Figure 1). In session one, participants completed the videoconference version of the MoCA. Eligible participants then filled out a sociodemographic and health questionnaire via Qualtrics (RRID: SCR_016728), an online questionnaire tool. In session two, participants began with the immediate recall of two Taler stories (38), followed by 20 minutes of various cognitive measures (omitted from this paper), including the Survey of Autobiographical Memory (SAM; 40), and then performed the delayed recall of the Taler Stories and the VPA (50) on Gorilla (RRID: SCR_020991), an online research platform. The National Aeronautics and Space Administration

Task Load Index (NASA-TLX) was completed after each task, except the SAM (51). All tasks were adapted for online administration, with auditory stimuli pre-recorded and participants' spoken responses recorded via Gorilla. Throughout, participants remained connected on Zoom, with a research team member available for technical support.

Figure 1. *Schematic of the study design.* Abbreviations: cISPR, community Integrated System of Participation in Research at the University of Ottawa; DR, delayed recall; MoCA, Montreal Cognitive Assessment; IR, immediate recall; n, sample size; NASA-TLX, National Aeronautics and Space Administration Task Load Index; ORCF, Ottawa Regional Cancer Foundation; SAM, Survey of Autobiographical Memory; VPA, Verbal Paired Associates.



2.3 Measures

2.3.1 Montreal Cognitive Assessment (MoCA)

The MoCA is a 13-item cognitive screening tool designed to detect mild cognitive impairment by evaluating memory, attention, language, executive functioning, and visuospatial abilities (48). Scores from each item are summed to yield a total score on 30, with lower scores indicating greater cognitive impairment. A cut-off score of ≤21 was applied for this study, as the standard cut-off of 26 may lead to over-pathologizing cognitive difficulties in this clinical population (52).

2.3.2 Taler Stories

The Taler Stories task is designed to assess episodic verbal memory (38) and was developed as an alternative to WMS - LM (53) to refine scoring criteria, enhance interpretation of group differences, and improve inter-rater reliability (38). For this study, one pair from the 12 Taler Stories pairs was randomly selected. Participants listened to two stories, each comprised of four sentences totaling 65 to 69 words, then recalled them immediately and again after a 20-minute delay. Responses were scored as verbatim (exact word-for-word recall), gist (accurate, rephrased content), or distortion (inaccurate details). For example, "*One sunny Saturday, Fred and Grace went to visit their two grandchildren in New York*", would be scored as: "went to visit" is verbatim, "went to see" is gist, and "went to pick up" is a distortion. Each story contains 50 informational units, which are scored separately to generate verbatim, gist, and distortion scores—each with a maximum of 50 points. A high verbatim score reflects greater recall of episodically rich and specific details, a high gist score indicates accurate recall of the story's general content and themes, whereas a high distortion score reflects inaccurate recall of story content. A retrieval success score was calculated by summing verbatim and gist scores and subtracting distortions to capture total accurate recall while accounting for errors.

2.3.3 Verbal Paired Associates (VPA)

The VPA task is a widely used measure of verbal episodic memory (50). Participants listened to a list of eight unrelated word pairs (e.g., banana-shoe). Afterward, they heard one word from each pair (e.g., banana) and were asked to recall the corresponding target word (e.g., shoe). The procedure was repeated across four trials, with the stimuli presented in a fixed, trial-specific sequence. The total score out of 32 was derived by summing the correct responses for each word pair across all four trials, with lower scores indicating worse episodic recall.

2.3.4 Survey of Autobiographical Memory (SAM)

The SAM is a 26-item self-report questionnaire designed to assess perceived abilities related to episodic, semantic, future, and spatial memory (49). Participants rated each item using a 4-point Likert scale (strongly disagree to strongly agree). Each item response was converted to a numerical score based on an established scoring procedure (49). Domain-specific scores were calculated by summing relevant items, with higher scores indicating better perceived memory functioning. For this study, only episodic and semantic subscales were analyzed.

2.3.5 National Aeronautics and Space Administration Task Load (NASA-TLX)

The NASA-TLX is a self-report measure designed to assess cognitive workload during tasks (51). The 6-item questionnaire evaluates various domains of workload: mental demand, physical demand (omitted from this study), temporal demand, performance, effort, and frustration. Participants rated each item on a 20-point scale, which was summed to yield a maximum score of 100, with higher scores indicating higher perceived cognitive workload.

2.4 Statistical Analysis

Responses were manually transcribed, scored, and double-checked by study researchers blind to conditions. Inter-rater reliability for the Taler Stories scoring exceeded 90%, with scoring discrepancies resolved through discussion. Statistical analyses were conducted using SPSS 28 (RRID:SCR_002865). Four 2 x 2 repeated measures ANOVAs (RM ANOVA) assessed four

memory recall types on the Taler Stories (verbatim, gist, distortions, retrieval success) across time (immediate vs. delayed) for both groups (BCS vs. NC). Bonferroni correction for multiple comparisons was applied when necessary to reduce the risk of type I errors. Independent samples t-tests compared group performance on the VPA, SAM, and NASA-TLX. Pearson correlations (*r*) assessed the relationship between: NASA-TLX and Taler Stories - Immediate Recall, NASA-TLX and Taler Stories - Delayed Recall, and NASA-TLX and VPA. Statistical significance was set at $\alpha = .05$, and partial eta squared (ηp^2) was calculated to estimate effect sizes. Figures were generated using GraphPad Prism (RRID:SCR_002798). Final sample sizes varied by task due to missing data: Taler Stories ($n = 83$; BCS = 42, NC = 41), SAM ($n = 87$; BCS = 45, NC = 42), and VPA ($n = 88$; BCS = 45, NC = 43).

3. Results

3.1 Taler Stories

Verbatim: RM ANOVA revealed a main effect of group [$F(1,81) = 5.88$, $p = .02$, $\eta p^2 = .06$], with BCS recalling fewer verbatim details than NC. No main effect of time [$F(1,81) = 3.48$, $p = .06$, $\eta p^2 = .04$] or time X group interaction [$F(1,81) = 1.85$, $p = .17$, $\eta p^2 = .02$] were observed (Figure 2).

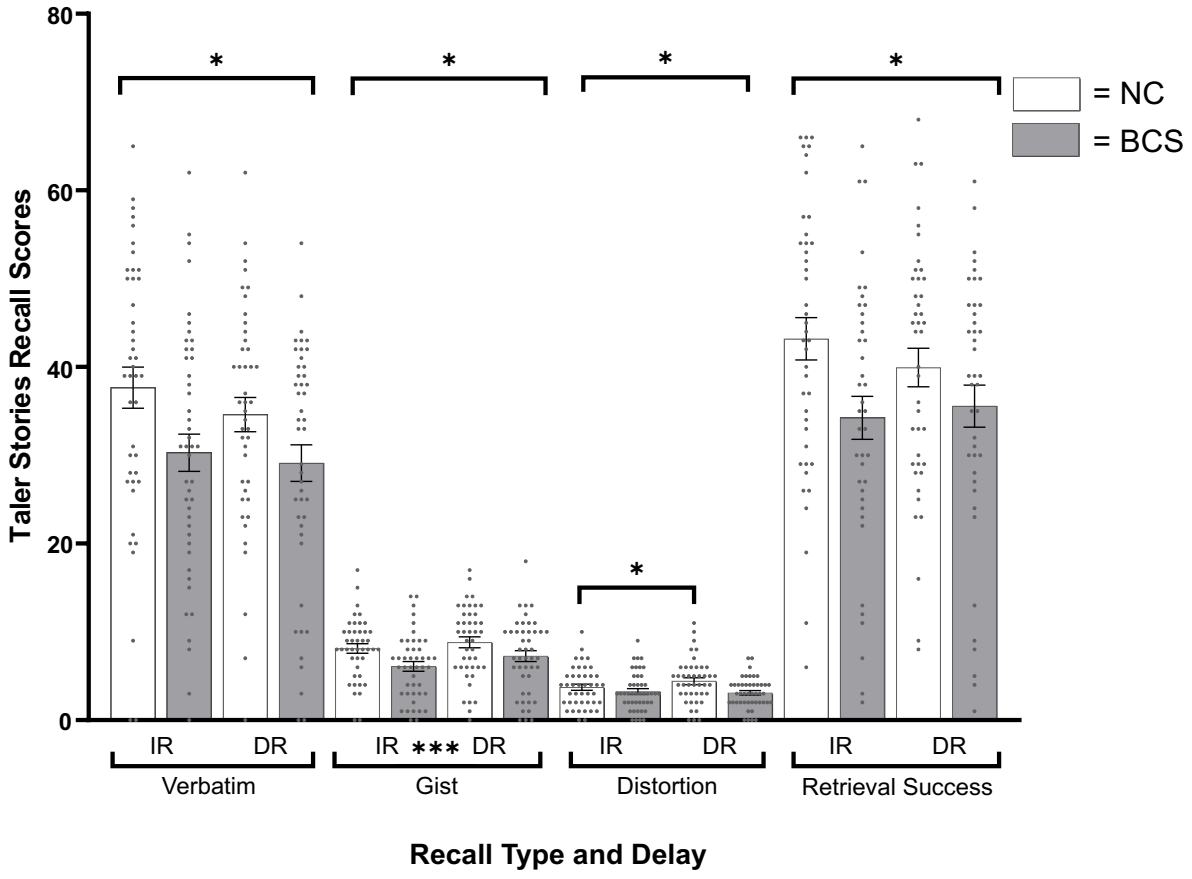
Gist: A main effect of group [$F(1,81) = 5.82$, $p = .02$, $\eta p^2 = .06$] and time [$F(1,81) = 12.31$, $p < .001$, $\eta p^2 = .13$] emerged, with BCS reporting fewer gist details relative to NC, and both groups reporting more gist details during delayed recall compared to immediate recall. No time X group interaction was observed [$F(1,81) = .49$, $p = .48$, $\eta p^2 = .006$; Figure 2].

Distortion: A main effect of group [$F(1,81) = 4.08$, $p = .04$, $\eta p^2 = .04$], with BCS reporting fewer distortions relative to NC, and a group X time interaction [$F(1,81) = 4.24$, $p = .04$, $\eta p^2 = .05$] was observed. Post-hoc analyses identified more distortions committed by NC relative to BCS during delayed recall ($p = .008$), but similar performance during immediate recall ($p = .34$). Additionally, NC committed significantly more distortions over time ($p = .02$), whereas BCS

showed no time-related difference (p = .61). No main effect of time [F(1,81) = 1.75, p = .18, ηp^2 = .02] was observed (Figure 2).

Retrieval success: A main effect of group [F(1,81) = 5.58, p = .02, ηp^2 = .06] revealed that BCS reported fewer total correct story details compared to NC. No main effect of time [F(1,81) = .48, p = .49, ηp^2 = .006] or time X group interaction [F(1,81) = - 3,65, p = .06, ηp^2 = .04] were observed (Figure 2).

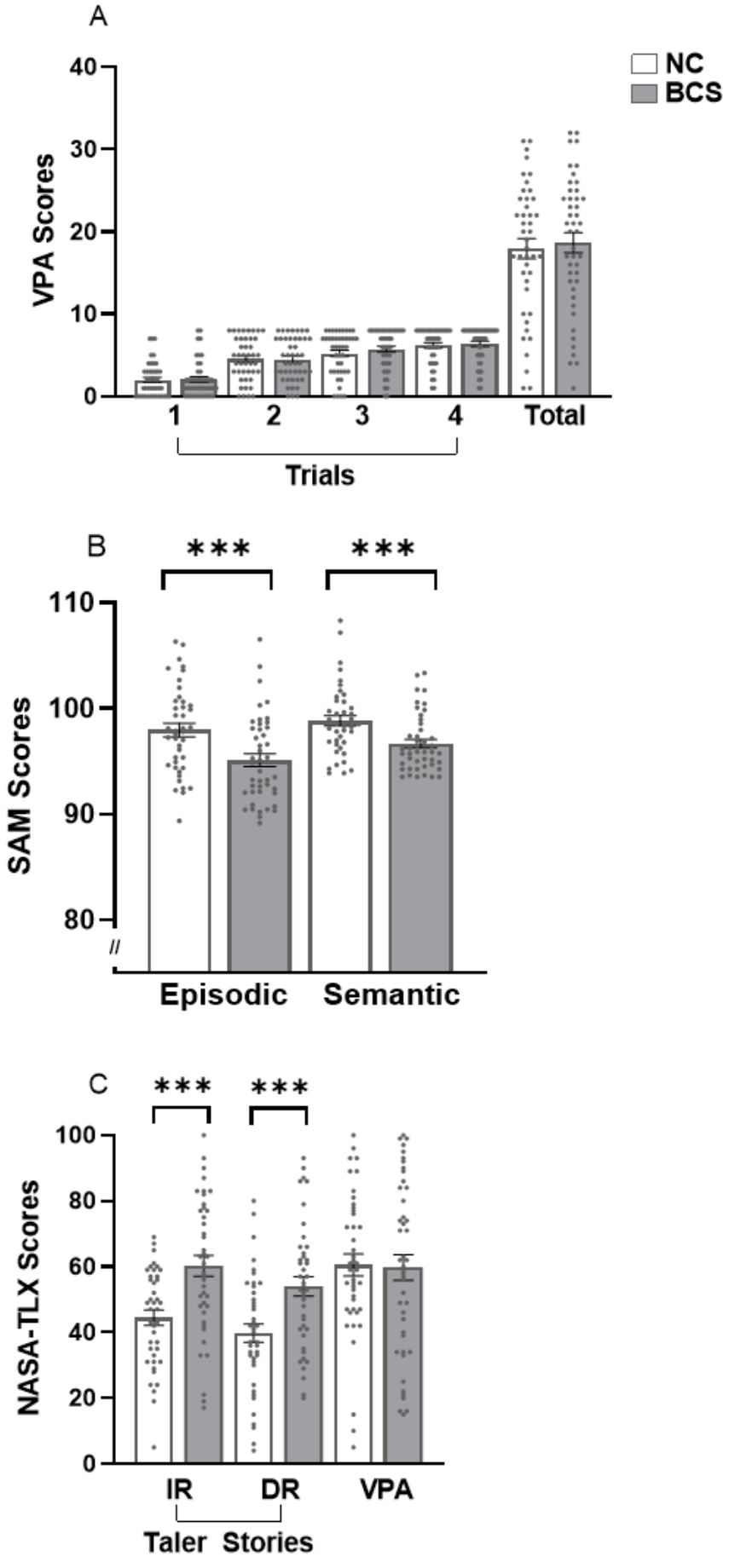
Figure 2. *Breast cancer survivors and non-cancer controls performance on the Taler Stories.* Grey bars represent breast cancer survivors, white bars represent non-cancer controls, error bars indicate the standard error of the mean (SEM), and individual data points are overlaid in light grey. Significant stars at the top represent main effects of group, in the middle represents a significant interaction, and between IR and DR represents a main effect of time. * denotes p < .05 level and *** denotes p < .001. Abbreviations: BCS, breast cancer survivor; NC, non-cancer controls; IR, immediate recall for Taler Stories; DR, delayed recall for Taler Stories.



3.2 Verbal Paired Associates

An independent sample t-test identified comparable VPA memory between groups (t_{86} = .41, p = .34). No group differences were observed within each of the four individual VPA trials (all p's > .05; Figure 3A).

Figure 3. *Breast cancer survivors and non-cancer controls performance on the cognitive measures. (A) Verbal Paired Associates (VPA), (B) Survey of Autobiographical Memory (SAM), and (C) National Aeronautics and Space Administration Task Load Index (NASA-TLX).* Grey bars represent breast cancer survivors, white bars represent non-cancer controls, error bars indicate the standard error of the mean (SEM), and individual data points are overlaid in light grey. *** denotes p < .001. Abbreviations: BCS, breast cancer survivor; NC, non-cancer controls; IR, immediate recall for Taler Stories; DR, delayed recall for Taler Stories; NASA-TLX, National Aeronautics and Space Administration Task Load Index; SAM, Survey of Autobiographical Memory; VPA, Verbal Paired Associates.


A
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90
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Episodic
Semantic
C
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NASA-TLX Scores
100
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60
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IR
DR
VPA
Taler Stories

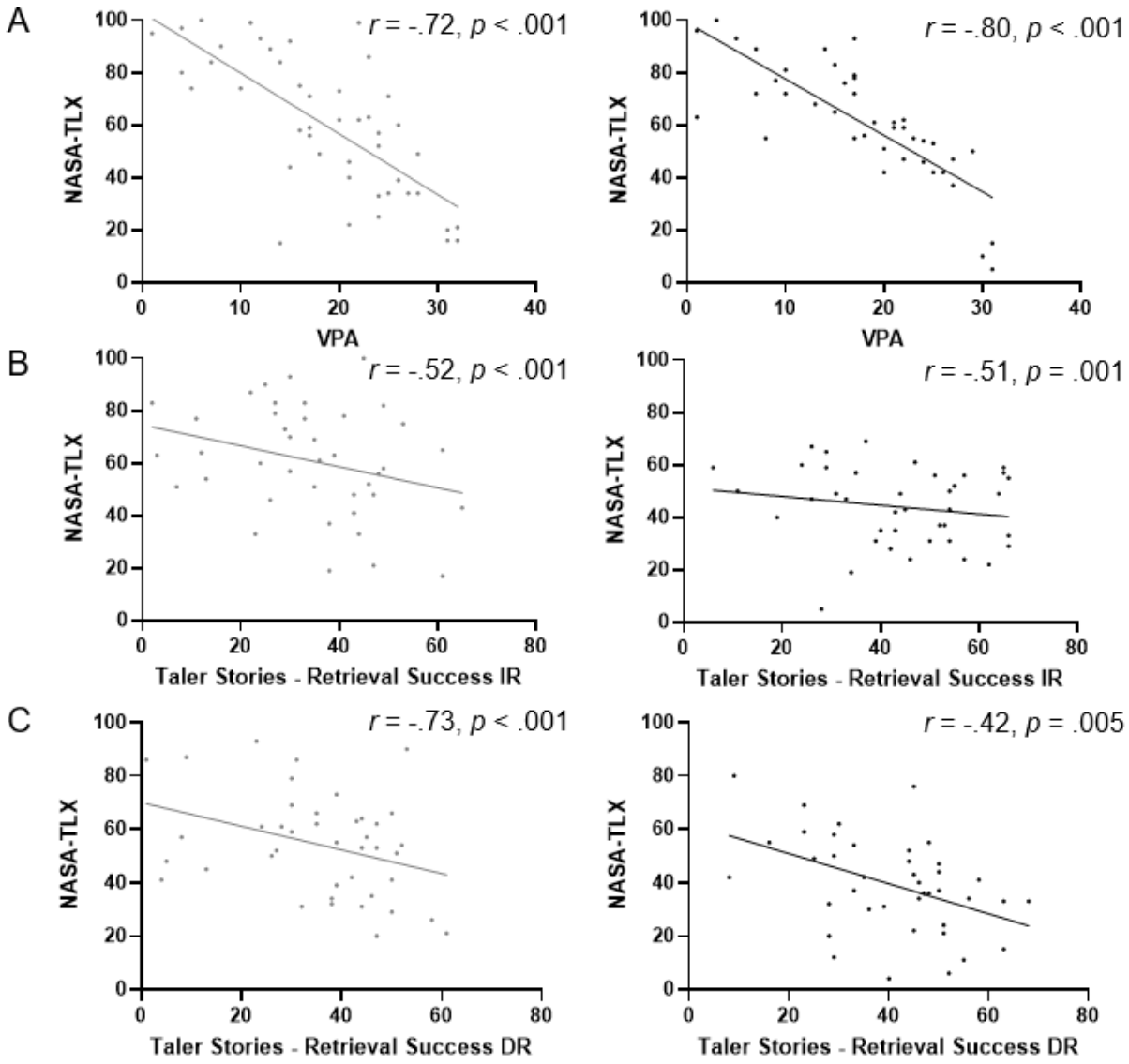
3.3 Survey of Autobiographical Memory

BCS rated higher subjective difficulties with their episodic (t_{85} = -3.25, p < .001) and semantic (t_{85} = -3.38, p < .001) memory abilities compared to NC (Figure 3B).

3.4 Cognitive Workload

BCS reported more cognitive effort than NC during both the immediate (t_{81} = 4.02, p < .001) and delayed (t_{81} = 3.52, p < .001) recall phases of the Taler Stories task (Figure 3C). However, comparable ratings of cognitive effort were reported by both groups for the VPA task (t_{86} = -.14, p = .44; Figure 3C). Correlational analyses revealed higher cognitive workload was associated with poorer task performance on the following: VPA (BCS, r_{43} = -.72, p = .005; NC, r_{41} = -.80, p < .001; Figure 4A); successful retrieval during Taler Stories immediate recall (BCS, r_{40} = -.52, p < .001; NC, r_{39} = -.51, p = .001; Figure 4B); successful retrieval during Taler Stories delayed recall (BCS, r_{40} = -.73, p < .001; NC, r_{39} = -.42, p = .005; Figure 4C).

Figure 4. *Correlations. (A) NASA-TLX and VPA, (B) NASA-TLX and Taler Stories Successful Retrieval for Immediate Recall, (C) NASA-TLX and Taler Stories Successful Retrieval for Immediate Recall.* Grey bars/figures on the left represent breast cancer survivors, black bars/figures on the right represent non-cancer controls. Abbreviations: IR, immediate recall for Taler Stories; DR, delayed recall for Taler Stories; NASA-TLX, National Aeronautics and Space Administration Task Load Index; SAM, Survey of Autobiographical Memory; VPA, Verbal Paired Associates.



4. Discussion

This study examined the long-term effects of cancer treatment on episodic memory in BCS, using both narrative and standardized VPA tasks. Uniquely, it is the first to assess recall of verbatim, gist, and distortion details of narrative event memories in this population. As hypothesized, BCS showed impaired performance on the narrative memory task and reported greater cognitive workload compared to NC. In contrast, their performance on the VPA task was comparable to that of NC, with no reported increase in cognitive workload to complete this task. These findings were contrary to our expectations, and highlight an important limitation to

standardized memory tasks that may contribute to an under-reporting of cognitive impairment following cancer treatment.

BCS recalled fewer verbatim and gist-based details on a naturalistic memory task compared to NC. Despite these differences, both groups performed similarly across immediate and delayed recall, suggesting similar patterns of forgetting even over a brief period of 20 minutes. These findings are noteworthy given that verbatim memory typically declines over time, even in healthy individuals (54). Both groups recalled more gist details after a delay, consistent with memory becoming more gist-like and schematic over time (12), a finding that is also observed over longer periods of weeks and months. An unexpected finding was survivors reporting fewer gist details than NC, potentially indicating generally less accessible memory content (55). Interestingly, only NC had a significant increase in memory distortions over time. These results support prior findings of cancer survivors recalling fewer narrative details (30,56,57), but contrast with studies showing no effects of chemotherapy (32,58). Accounting for memory distortions, BCS recalled fewer accurate gist and verbatim details than NC—a difference that remained consistent over time.

The present findings align with those of Taler et al. (2020) (38) who developed this narrative task to assess episodic memory quality in both healthy aging and in cases of mild cognitive impairment (MCI). Our results indicate that both BCS and NC groups reported fewer verbatim details following the delay, mirroring the pattern observed by Taler et al. when comparing healthy younger and older adults. Overall, younger adults produced more verbatim details than older adults, who in turn outperformed individuals with MCI. This pattern parallels our observation that NC participants reported more verbatim details than BCS participants, which potentially suggests that BCS may follow an accelerated trajectory of age-related memory changes, mirroring patterns seen in typical aging (59).

The finding that NC reported more memory distortions relative to BCS is counterintuitive but identifies an interesting distinction. Rather than reflecting superior memory accuracy, the lower distortion and gist scores among BCS likely indicate impairments in memory encoding (30,32).

While memory naturally transforms over time, becoming less specific and more prone to distortion particularly for schema-consistent events, BCS may encode fewer details from the outset, leaving less information available for later recall or distortion (11,12,21). This interpretation is reinforced by lower overall recall and supported by retrieval success scores, which account for both accuracy and completeness of memory.

In contrast to the narrative memory task, BCS and NC performed similarly on the VPA. This suggests that certain aspects of episodic memory, particularly simple associative learning, may remain relatively preserved following treatment. These findings align with prior findings that VPA performance lacks the sensitivity to detect subtle cognitive deficits, even in individuals with MCI (60).

BCS reported greater cognitive effort than NC during narrative recall, but not during the VPA task, suggesting that more complex, real-world memory tasks place higher cognitive demands on BCS. This pattern implies that BCS may recruit additional cognitive resources through compensatory mechanisms to perform narrative recall tasks (61,62). However, across both groups, higher subjective cognitive effort was associated with worse memory performance, indicating that these impressions likely reflect awareness of cognitive challenges (63). BCS also reported greater subjective difficulties with both episodic and semantic memory, consistent with previous research identifying persistent perceived memory problems following treatment (64,65).

Methodological variability likely contributes to inconsistencies in the literature on chemotherapy-related cognitive impairment, including differences in participants, treatment type and dosage, time since treatment, and measures. While many studies find that chemotherapy-treated cancer survivors perform worse on neuropsychological tests and report more memory and concentration difficulties, these subjective complaints often correlate more strongly with psychological distress than with objective impairment (39,66). Additionally, survivors who had above-average cognitive abilities before treatment may still score within normal ranges post-treatment but feel they have declined compared to their personal baseline. Thus, their concerns might reflect real changes that are not captured by standard population-based comparisons (39).

Both perceived and objective cognitive difficulties should be routinely addressed throughout cancer survivorship, with regular screening across different stages of recovery (67,68). Although clinical resources may be limited, comprehensive pre- and post-treatment neuropsychological assessments that incorporate standardized and ecologically valid measures, and subjective measures of cognitive functioning are recommended to define cognitive profiles and guide interventions (65,69–71). This ongoing approach can help validate patient experiences and support appropriate management of cognitive challenges over time (67).

Limitations

Our online cross-sectional design enabled recruitment of a geographically diverse Canadian sample, including immunocompromised participants. However, reliance on social media recruitment may have biased the sample toward younger, Caucasian groups (72,73), resulting in limited diversity and reduced generalizability. Computerized cognitive assessments allow for standardized administration, enhanced accessibility, feasibility, and participant comfort in a familiar environment (74,75). Although this can introduce variability related to environment, fatigue, distractions, and technology (74,75), this was mitigated by conducting sessions via Zoom with a trained researcher present throughout the study. Additionally, although treatment-related factors are known to influence cognition (3), unavailable or incomplete patient-reported treatment details prevented covariate analyses, limiting considerations of their influence on cognitive outcomes. Future research should collect detailed medical data to clarify mechanisms underlying cancer-related cognitive dysfunction. Additionally, longitudinal design that include pre-treatment cognitive and neuroimaging assessments would enable stronger causal inferences about the emergence and development of treatment-related cognitive and neural changes.

5. Conclusion

This study adds to evidence of persistent cognitive challenges among BCS, specifically in episodic memory. By contrasting a naturalistic narrative task with a standardized memory task, we show that traditional assessments may overlook real-world memory difficulties. Ecologically

valid measures that better reflect survivors' lived experiences paired with a cognitive workload measure provide a more nuanced view of both memory function and the subjective effort required to complete everyday tasks. These results underscore the need for multidimensional cognitive assessments in survivorship care and support the development of tailored interventions that validate survivors' experiences and enhance quality of life.

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CHAPTER 5

Cancer Treatment and Memory in Breast Cancer Survivors: Differential Effects on Detailed Episodic and Gist-Like Memory Recall Over Time

Meenakshie Bradley-Garcia[1], Hamed Neveu Karimpour[1], Defne Oksit[1], Mitchell Lilley[1], Chloé Cateaux[1], Annick F. Tanguay[1], Melanie J. Sekeres[1]

[1]School of Psychology, University of Ottawa, Ottawa, Ontario, Canada

Authors note

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Abstract

Breast cancer survivors (BCS) frequently experience chemotherapy-related cognitive impairment, including episodic memory deficits. This study examined the long-term impact of cancer treatment on memory for naturalistic events, using film clips to assess recall of central (gist-like elements; reflects the story narrative) and peripheral (episodic elements; sensory or contextual details related to the event) details. While memory for both types of details typically decline over time, peripheral details are especially vulnerable to decline, and are sensitive to impairment in individuals with medial temporal lobe disruption. Participants (BCS, n = 42; non-cancer controls, NC, n = 41) viewed 40 short film clips (encoding). Memory for the clips' content was tested at two timepoints: immediately following encoding (20 clips; immediate retrieval) and after a 7-day delay (20 clips; delayed retrieval). BCS recalled significantly fewer peripheral details than NC, whereas recall of central (gist-like) information did not differ between groups. No group differences were observed across individual sub-categories of peripheral details, temporal sequencing, or the rate of forgetting over the 7-day delay. Subjective memory ratings mirrored objective performance, with BCS reporting lower memory vividness than NC, while reporting comparable memory for story content. These findings suggest that chemotherapy may reduce the overall richness of episodic event representations while preserving central, schematic aspects of memory and the temporal organization of events. Naturalistic memory paradigms that assess the qualitative features of event memory may provide a sensitive approach for detecting subtle treatment-related cognitive changes in cancer survivors.

Keywords: breast cancer, chemobrain, episodic memory, cancer survivorship, memory

1. Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide (Freihat et al., 2025). Chemotherapy remains one of the most effective cancer treatments, significantly improving patient survival (Brianna & Lee, 2023). However, despite its therapeutic benefits, chemotherapy is associated with a high prevalence of adverse cognitive side-effects. Up to 75% of patients report experiencing chemotherapy-related cognitive impairments, often referred to as "chemobrain", a condition that can persist for years and potentially decades after treatment (Koppelmans et al., 2012; Nakamura et al., 2019; Vardy & Tannock, 2007). Chemotherapy-related cognitive impairments typically involve deficits in memory, attention, processing speed, and executive function (Ahles et al., 2012; Amani et al., 2024; Bradley-Garcia et al., 2022; Jansen et al., 2011; Wefel et al., 2004). These impairments can interfere with daily activities and significantly reduce quality of life in cancer survivors (Janelsins et al., 2014; Reid-Arndt et al., 2009).

While chemotherapy remains central to cancer treatment, its neurotoxic effects, dependent on factors such as drug type, dosage, and administration frequency, pose serious risks to cognitive and brain health (Sekeres et al., 2021; Yang & Moon, 2013). Many chemotherapeutic agents used to treat non-central nervous system cancers, including breast cancer, can cross the blood-brain barrier, where they are capable of inducing neuroinflammation and neuronal death (Wardill et al., 2016). These effects are especially detrimental to medial temporal lobe structures including the hippocampus (Alhowail, 2025; Bagnall-Moreau et al., 2019; Winocur et al., 2018a). The hippocampus plays a critical role in encoding and retrieval of episodic memory, memories for unique events occurring at a specific time and place (Eichenbaum et al., 1999; Tulving, 2002).

The hippocampus remains critical for retrieving richly detailed episodic memories. However, as memories age, their perceptual and contextual details gradually fade as the representation becomes more schematic and gist-like. As this transformation occurs, retrieval becomes less dependent on hippocampal processing and increasingly supported by a distributed neocortical

network, including the medial prefrontal cortex (mPFC) (Gilboa & Moscovitch, 2021; Sekeres et al., 2018, 2024; Tarder-Stoll et al., 2026). In the intact brain, both hippocampally-mediated episodic representations and mPFC-mediated schematic representations of an event can co-exist, with each representation relying on their respective neural systems and being accessed as needed. In cases of hippocampal dysfunction, however, the episodically-detailed version of the event memory is susceptible to loss or is less likely to become encoded in the first place, making those richly detailed elements of an event memory unavailable at retrieval (Sekeres et al., 2018; Tarder-Stoll et al., 2026).

Episodic memory plays a vital role in everyday life by enabling people to interpret present experiences in light of past events (Tulving, 1993). Within episodic memories, the temporal sequence of events is encoded to support coherent, detailed representations of complex experiences (Eichenbaum, 2013; Howard & Eichenbaum, 2015; Lehn et al., 2009; Sugar & Moser, 2019). However, traditional episodic memory measures used in assessments of cognitive disorders typically employ discrete stimuli, such as word lists or paired-associates tasks, which fail to reflect the complexity and contextual richness that characterize real-life events (Davachi & Dobbins, 2008). To increase the ecological validity of episodic memory assessments, there has been a shift towards the use of naturalistic stimuli, such as movies, narratives, or stories, that better reflect everyday memory demands. These approaches contain the schematic structure of real world episodes that are not captured by standardized lab-based tasks, which typically involve artificial associations between unrelated items (e.g., apple-pen) (Bailey & Smith, 2024; Chen et al., 2016, 2017; Ezzyat & Davachi, 2011; Fenerci et al., 2025; Lee et al., 2020; Penaud et al., 2023; Taler et al., 2020).

Naturalistic event memories can be broken down into their central and peripheral components (Heuer & Reisberg, 1990; Sekeres et al., 2016, 2018). Central details capture the core elements essential to an event's story line (e.g., a family having dinner at a restaurant), whereas peripheral details include descriptive or sensory information related to the event but not essential to the narrative (e.g., color of the walls, location of table in the room, sound of the

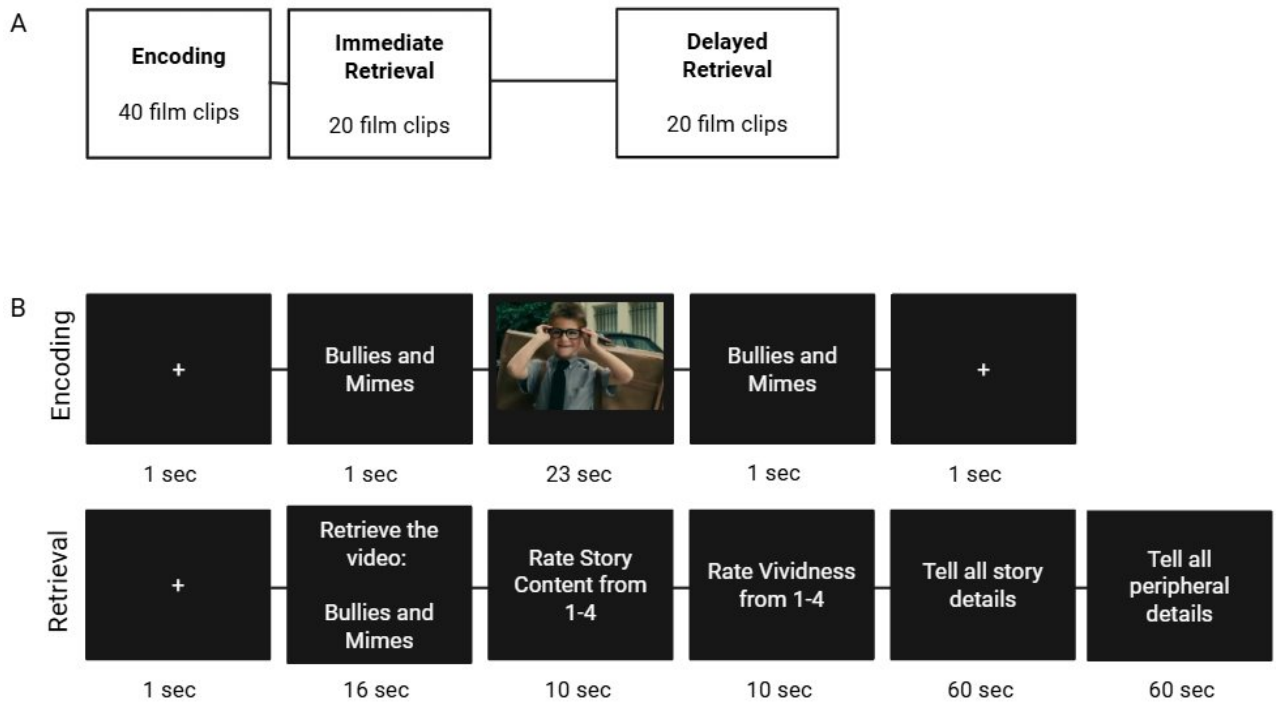
server's voice). These categories broadly correspond to gist-like and schematic elements, and episodically detailed elements, respectively. Peripheral details encompass visual information (object, scene, spatial details, colors), auditory features (background noises, music), and contextual aspects (time of day, weather). Although memory for both central and peripheral details decline over time, peripheral information is especially vulnerable to memory loss. This pattern has been consistently observed in narrative and film-based memory paradigms (Conway et al., 1991; Furman et al., 2007; Sekeres et al., 2016, 2018), which identify how memory for naturalistic events changes as it becomes less perceptually detailed and more gist-like or schematic. Because these paradigms rely on richly detailed episodic retrieval, they are sensitive to detecting subtle memory impairments associated with hippocampal dysfunction (Hayes et al., 2004; St-Laurent et al., 2014, 2016). Consistent with this, individuals with medial temporal lobe damage show disproportionate impairments in recalling peripheral elements of episodic memories (Gilboa et al., 2006; Rosenbaum et al., 2005; Steinvorth et al., 2005; St-Laurent et al., 2009).

Chemotherapy-related memory impairments in breast cancer survivors are well-documented (Ahles et al., 2012; Amani et al., 2024; Bradley-Garcia et al., 2022; Jansen et al., 2011; Wefel et al., 2004). However, most assessments rely on standardized neuropsychological tests, which are limited in their ability to assess complex, naturalistic episodic memory. These measures rarely use ecologically valid stimuli to examine how the content and temporal organization of memory for real-life events change over time following treatment. Consequently, little is known about how chemotherapy affects the qualitative content of memory for richly detailed, everyday experiences.

The present study addresses this gap by assessing episodic memory for naturalistic events in breast cancer survivors using short film clips depicting everyday scenarios. We predicted that breast cancer survivors would show selective impairments in recalling peripheral (perceptually rich, episodic) details, with relative preservation of central (gist-like, schematic) information compared with non-cancer controls. Building on evidence that episodic details decline more

steeply than central information (Conway, 2001; Robin & Moscovitch, 2017; Sekeres et al., 2018), we tested whether this vulnerability is exacerbated in women with a history of breast cancer who completed cancer treatment. We also examined whether specific sub-types of peripheral information (perceptual, auditory, spatial) are differentially affected by chemotherapy. Finally, given the hippocampus's critical role in representing the sequential structure of events, we predicted that breast cancer survivors would have reduced accuracy when recalling the temporal order of events relative to controls. To test these ideas, we compared recall of central and peripheral details immediately after encoding and following a 7-day delay (Figure 1A,B).

Figure 1. *Schematic representation of the Film Clip Task.* (A) Experimental timeline, and (B) schematic of the study design in the encoding session (top) and retrieval sessions (bottom).



2. Methods

2.1 Participants

We recruited female breast cancer survivors (BCS), aged 30 to 65, who completed treatment at least six months prior to participation, and age-matched women without a history of cancer (non-cancer controls, NC). Participants were recruited through community outreach, public

advertisements on social media, the community Integrated System of Participation in Research at the University of Ottawa, and the Cancer Foundation Maplesoft-Jones Centre at the Ottawa Regional Cancer Foundation. Exclusion criteria included: (1) a mental health diagnosis within the past 12 months, (2) a lifetime diagnosis of brain injury (e.g., concussion), neurodevelopmental (e.g., attention-deficit/hyperactivity disorder), or neurological (e.g., stroke) disorder, (3) initiation of new mood-altering medications within the past 12 months, (4) current substance dependence or consuming cannabis more than 7 times per month, (5) non-fluent in English, (6) residence outside of Canada, and (7) a score indicative of mild or major cognitive impairment on the Montreal Cognitive Assessment (MoCA; i.e., ≤20). Of the ninety-three eligible participants, five were lost to attrition (BCS, *n* = 5; NC, *n* = 0) and five were excluded due to audio recording failure (BCS, *n* = 2; NC, *n* = 3), resulting in a final sample of 83 participants (BCS, *n* = 42; NC, *n* = 41; Tables 1 and 2). This study received full board review and approval from the University of Ottawa's Research Ethics Board (H-04-21-6706) and was conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Table 1. *Participant demographic information.* Abbreviations: BCS, breast cancer survivors; NC, non-cancer controls; M, mean; n, sample size; SD, standard deviation; %, percentage.

	BCS (*n* = 42)	NC (*n* = 41)
	M (*SD*) or % (*n*)	M (*SD*) or % (*n*)
Age	51.2 (8.8)	49.5 (10.8)
Province of residence		
Alberta	0.0% (0)	4.9% (2)
British Columbia	2.4% (1)	7.3% (3)
Manitoba	9.5% (4)	0.0% (0)
New Brunswick	2.4% (1)	0.0% (0)
Nova Scotia	4.8% (2)	0.0% (0)
Northwest Territories	2.4% (1)	0.0% (0)
Ontario	59.5% (25)	70.7% (29)
Prince Edward Island	2.4% (1)	0.0% (0)
Quebec	11.9% (5)	12.2% (5)
Saskatchewan	4.8% (2)	2.4% (1)
Yukon	0.0% (0)	2.4% (1)
Race		
White	95.2% (40)	82.9% (34)
Black	0.0% (0)	2.4% (1)
Greek	2.4% (1)	0.0% (0)
East Asian	0.0% (0)	2.4% (1)
South Asian/East Indian	2.4% (1)	2.4% (1)
Indigenous	0.0% (0)	2.4% (1)
Latin American	0.0% (0)	2.4% (1)
Person of mixed origin	0.0% (0)	2.4% (1)
West Asian, North African, Arab	0.0% (0)	2.4% (1)
I prefer not to answer	0.0% (0)	2.4% (1)
Completed Education Level		
High school diploma	4.8% (2)	2.4% (1)
College degree	26.2% (11)	19.5% (8)
Bachelor's degree	45.2% (19)	39.0% (16)
Master's degree	19.0% (8)	26.8% (11)
Doctorate degree	0.0% (0)	0.0% (0)
Other	4.8% (2)	4.8% (2)
Household Income		
< $30 000	0.0% (0)	7.3% (3)
$30 000 - $50 000	2.4% (1)	9.8% (4)
$50 000 - $100 000	26.2% (11)	19.5% (8)
$100 000 - $200 000	45.2% (19)	39.0% (16)
> $200 000	19.0% (8)	12.2% (5)
I prefer not to answer	7.1% (3)	12.2% (5)
Current Substance Use	42.9% (18)	58.5% (24)
Drug Frequency		
Daily	21.4% (9)	24.4% (10)
2-3 times per week	9.5% (4)	12.2% (5)
Once per week	2.4% (1)	9.8% (4)
Once per month	16.7% (7)	24.4% (10)
Not applicable	50.0% (21)	29.3% (12)
Mental Health Diagnosis (Lifetime)	11.9% (5)	14.6% (6)
Mental Health Symptoms (Past 6 months)	0.0% (0)	0.0% (0)
Mental Health Symptoms (Past 12 months)	0.0% (0)	4.9% (2)
Medications	81.0% (34)	48.8% (20)
Mood Altering Medications	14.3% (6)	7.3% (3)
Menopausal Status		
Pre-menopausal	21.4% (9)	48.8% (20)
Post-menopausal	78.6% (33)	51.2% (21)

Table 2. Breast cancer diagnosis and treatment details.

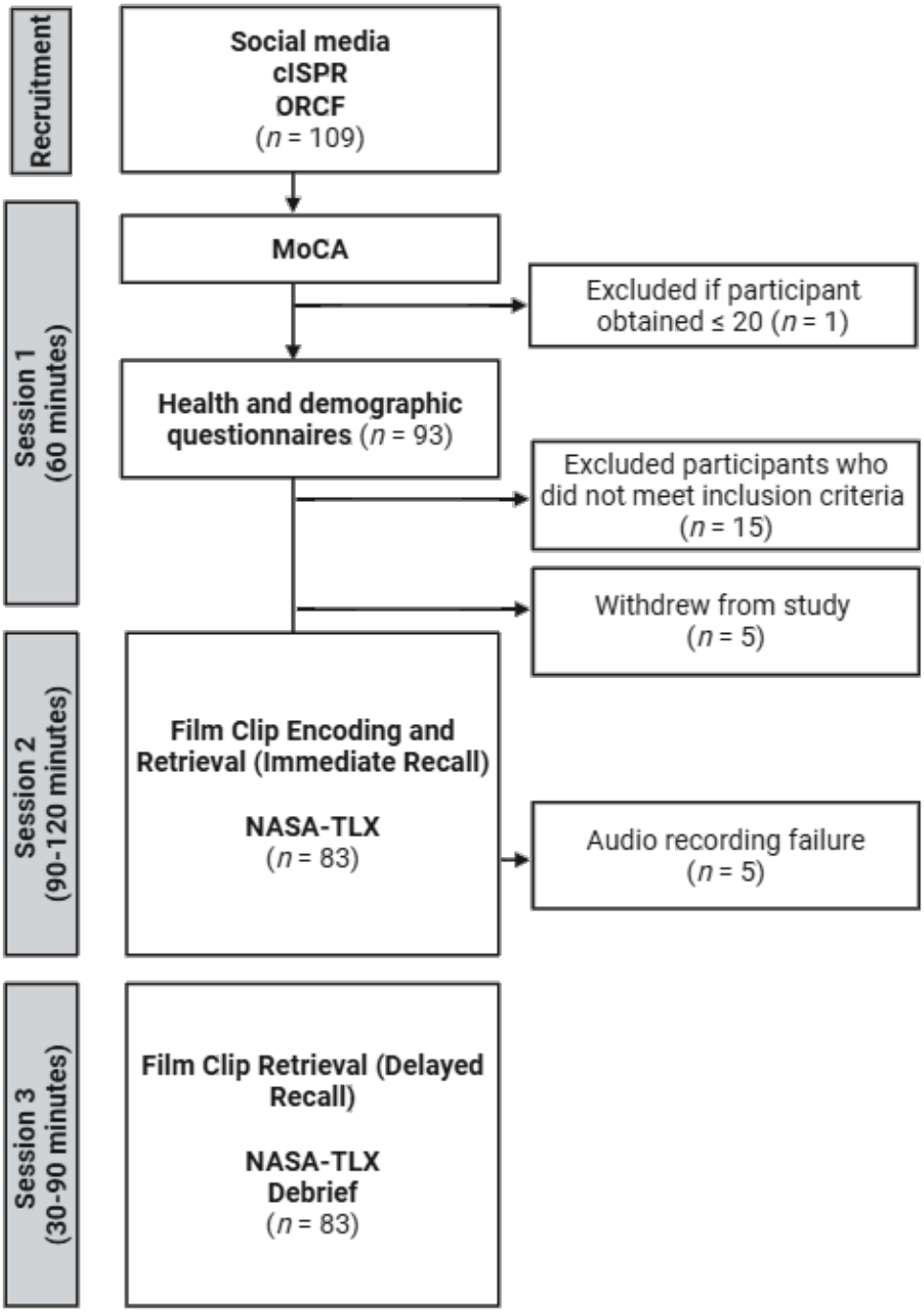
	Percentage (sample size)
Time Since Diagnosis	
1-2 years ago	16.7% (7)
2-5 years ago	50.0% (21)
5-10 years ago	19.0% (8)
>10 years ago	14.3% (6)
Cancer Stage at Diagnosis	
Stage 0	2.4% (1)
Stage 1	19.0% (8)
Stage 2	42.9% (18)
Stage 3	31.0% (13)
Unknown	4.8% (2)
Chemotherapy Treatment End	
6-12 months ago	16.7% (7)
1-2 years ago	26.2% (11)
2-5 years ago	28.6% (12)
5-10 years ago	19.0% (8)
>10 years ago	9.5% (4)
Current Hormone Therapy	
Yes	50.0% (21)
Not currently	7.1% (3)
Never	42.9% (18)
Treatment	
Chemotherapy	100.0% (42)
Hormonal Therapy	57.1% (24)
Radiation Therapy	78.6% (33)
Surgery	100.0% (42)
Immunotherapy	4.8% (2)
Targeted Therapy	19.0% (8)

2.2 Procedure

This study occurred over three online sessions (Figure 2). Session 1: Participants provided informed consent and completed the MoCA. Eligible participants completed a sociodemographic questionnaire through Qualtrics (RRID: SCR_016728), which collected demographic and health-related data. Session 2: Participants watched 40 short film clips (encoding), immediately recalled 20 clips (immediate retrieval, IR), then completed the NASA-TLX cognitive workload questionnaire. Session 3: Seven days later, participants recalled the remaining 20 clips (delayed retrieval, DR), and completed the NASA-TLX. Sessions 2 & 3 were conducted in Gorilla (RRID: SCR_020991), an online research platform. Participants completed all tasks while connected via

Zoom, a videoconferencing platform, with a member of the research team present to provide support. Participants were compensated with a gift card of their choice.

Figure 2. *Schematic representation of the study*. Abbreviations: cISPR, Integrated System of Participation in Research, community pool; ORCF, Ottawa Regional Cancer Foundation; MOCA, Montreal Cognitive Assessment; NASA-TLX, National Aeronautics and Space Administration Task Load Index; n, sample size.



2.3 Measures

2.3.1 Montreal Cognitive Assessment

The MoCA is a 13-item cognitive test designed to detect mild cognitive impairment (Nasreddine et al., 2005). It evaluates multiple cognitive domains including memory, attention, language, executive functioning, and visuospatial abilities. Scores from each item are summed to yield a maximum total score of 30, with a lower score indicating greater cognitive impairment. A cut-off score of ≤ 21 was applied for this study, as the standard cut-off score of 26 may lead to over-pathologizing cognitive difficulties in this patient population (Waldron-Perrine & Axelrod, 2012).

2.3.2 Film Clip Task

The Film Clip Task uses naturalistic event stimuli to assess the qualitative content of complex episodic memory. This measure is sensitive to differential memory loss for perceptually rich episodic memory details relative to more general central story details that capture the gist of the event, and which tend to be less impaired in individuals with medial temporal lobe damage (St-Laurent et al., 2014). The Film Clip Task occurred in two sessions: an encoding phase followed by an immediate retrieval phase (IR); and a delayed retrieval (DR) phase seven days later (Figure 1A, B). Foreign film clips (e.g., non-English language films) with limited dialogue were chosen to avoid memory enhancement effects of familiarity (Bonasia et al., 2018). The 40 film clips (each 23 s in duration) were divided into 4 series, with 10 clips per series. Each series was counterbalanced based on the film clips' visual complexity (e.g., color, background complexity, movement, number of background characters), story complexity (e.g., number of central characters, storyline complexity), sound complexity (e.g., speech, music, background noise), and emotional content (e.g., funny, surprising, sad, cute, quirky) (Sekeres et al., 2016). For both encoding and retrieval, clips were presented in a randomized order within each series, and participants were allowed a short self-timed break between series. See Figure 1A for the schematic design of the task.

Film Clip Encoding Session. Participants viewed pre-recorded instructional and demonstrational videos, followed by two practice encoding and retrieval trials guided by a study team member. Participants were told they would be subsequently tested on their memory for the clips following varying delays, and instructed not to rehearse the information in the interim. During encoding, participants watched 40 film clips. Each clip was given a title (e.g., "Boy, Girl and Balloon") that served as a retrieval cue in the recall task. The title appeared centrally on the screen for two seconds immediately before and after the clip played. Clips were centrally presented on a computer screen. Participants were instructed to pay attention to the title and content of each clip. A fixation cross was presented for one second between each clip.

Film Clip Retrieval Sessions. For retrieval, two series of clips (20 clips total) were pseudorandomly assigned to immediate or delayed retrieval. On each trial, the clip title appeared centrally on the screen as a cue for the participants to retrieve the corresponding clip. Participants were instructed to mentally replay the clip for 16 sec, then rate the amount of story content they recalled and the vividness of their memory on a 4-point Likert scale. Story content refers to the general plot line of the story ("what happened") (Berntsen & Rubin, 2002; St-Laurent et al., 2014). A rating of 1 indicated there was no story content in their memory, while 4 indicated they felt that their memory contained all of the story elements. Next, participants rated the vividness of their memory's perceptual content during retrieval. Perceptual content referred to visual (colors, lighting, textures, facial features, clothing, positions of objects, background details, weather, lighting conditions, etc.) and auditory (talking, laughing, background music, street sounds) details. Immediately following the ratings of each clip, participants were asked to verbally report the story content details they could recall from the clip (what happened, who did what, what was the situation; they were given a maximum of 60 seconds to report these details). Finally, participants were asked to verbally report the perceptual (visual or auditory) details they imagined while recalling the clip (up to 60 seconds). Seven days following immediate retrieval, participants completed the delayed retrieval task for the remaining 20 clips, following identical procedures. Audio recordings of the verbal retrieval trials were saved using Gorilla.

2.3.3 National Aeronautics and Space Administration Task Load Index

The National Aeronautics and Space Administration Task Load Index (NASA-TLX) is a self-report measure designed to assess perceived cognitive workload during a task (Hart & Staveland, 1988). The 6-item questionnaire evaluates various workload domains: mental demand, physical demand, temporal demand, performance, effort, and frustration. For the current study, the physical demand item was omitted due to the nature of the task. Following immediate and delayed retrieval task, participants rated each item on a 20-point scale, which was then summed to yield a maximum score of 100, with higher scores indicating a higher perceived cognitive workload.

2.4 Scoring

Self-report ratings of story and perceptual content were averaged across clips for each delay. The audio recordings for the story content and perceptual detail retrievals for each participant were manually transcribed then checked by a second member of the research team to ensure accuracy. Transcriptions were scored to categorize the central and peripheral details and double checked by a second team member. The scoring procedure followed the method described in Sekeres et al. (Sekeres et al., 2016), with additional subcategorization of peripheral details developed for this study. Scorers were blind to group conditions during scoring. Scored transcripts were quantified using customized scripts in R-Studio (RRID:SCR_001905).

Central detail scoring: Each film clip contained five to eight central story details describing its main events. Central details refer to the key elements that define an event's storyline, reflecting its gist and schematic structure. These details characterize the event's main plot and the actions or events that advance the plot. For each clip, central details were first scored for recall accuracy, regardless of their temporal sequence. Each correctly recalled central detail was coded as a correct response (cen-cor). Temporal accuracy was then evaluated. A correct response with correct temporality (cen-crct) indicated accurate recall of a central detail in the correct order. Errors of commission (cen-com) were identified when participants provided

details that were not present in the clip. Participants received a score of 1 for each central detail identified in any of these categories. Three study team members (MBG, DO, CC) reviewed each clip to score all central details. Inter-rater reliability of central detail scoring exceeded 90%, with scoring discrepancies resolved through discussion. See Table S1 for the complete list of central details (from St-Laurent et al., 2014), and Supplemental Material for an example of a coded transcript.

Peripheral detail scoring: Peripheral details include sensory and contextual information related to the event, such as visual, auditory, or contextual elements, but are not central to the plot. Unlike previous studies using this paradigm (Sekeres et al., 2016), the current study further categorized peripheral details into sub-types to allow examination of potential deficits in distinct episodic elements. Peripheral sub-details were scored using an adapted version of the Autobiographical Interview Scoring Manual (Addis et al., 2008; Levine et al., 2002; Renoult et al., 2019, 2020) modified for use with the Film Clip Task. For each clip, the total number of peripheral details was quantified. Seven peripheral detail sub-types were defined: event (per-event), place (per-place), time (per-time), auditory (per-a), object (per-o), object detail (per-od), and spatial (per-s) details (see Table S2 for operational definitions). These categories were selected because previous studies have reported that chemotherapy is associated with impairments in processing and recall of object and object-specific information (Li et al., 2018; Pergolizzi et al., 2019), spatial information (de Ruiter et al., 2011; Scherling et al., 2011), and auditory processing (Chattaraj et al., 2023; Dillard et al., 2022). In addition, event, place, and time details were included because they represent the core “what, where, when” components of episodic memory (Tulving, 2002). Participants received a score of 1 for each peripheral detail identified. No additional points were given for repeated details. Three study team members (MBG, HNK, ML) reviewed each clip to score all identifiable peripheral details, adding new valid details to the catalogue as needed based on participant responses. Inter-rater reliability of peripheral detail scoring exceeded 90%, with scoring discrepancies resolved through discussion. Peripheral detail errors were classified only as errors of commission (per-com),

reflecting a reported detail not contained within the film clip (see Supplemental Material for example of a coded transcript).

Forgotten clips: A clip was classified as forgotten (forg) when no central or peripheral details were reported in response to the title cue. A clip was classified as misremembered (cen-mix; per-mix) when its recollection was conflated with a different clip.

Retrieval success: The number of successfully recalled clips at each timepoint was calculated by subtracting forgotten and misremembered clips from the total number of clips per session: successfully recalled clips = 20 – (# forgotten clips + # mix clips). For each successfully recalled clip, a "retrieval success" score was calculated by subtracting the number of commission errors from the number of correctly recalled details per clip.

2.5 Statistical Analysis

Statistical analyses were conducted using SPSS 28 (RRID:SCR_002865). 2 x 2 repeated measures ANOVAs (RM ANOVA) were conducted to assess each central detail sub-type, with Time (immediate vs. delayed) as a within-subject factor, and Group (breast cancer survivors vs. non-cancer controls) as a between-subject factor. Separate 2 x 2 RM ANOVAs were conducted to assess each detail category, and NASA-TLX scores, and significant interactions were examined using Tukey post-hoc tests. Statistical significance was set at $\alpha = .05$, and partial eta squared (ηp^2) was calculated to estimate effect sizes. Bonferroni correction for multiple comparisons was applied when necessary. See Table S3 in the Supplemental Material for a chi-square analyses comparing demographic and health variables between groups. Figures were generated using GraphPad Prism (RRID:SCR_002798).

3. Results

3.1.1 Perceived Memory Ratings and Cognitive Workload

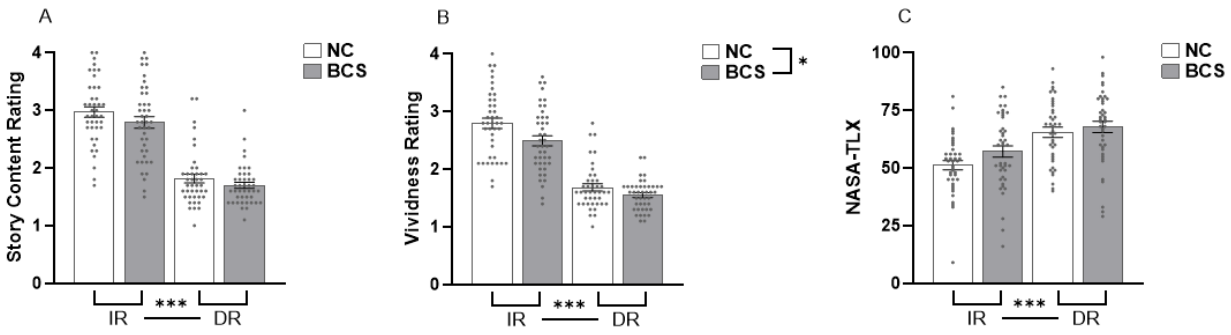
Participants rated their subjective recall of each clips' story content and the vividness of perceptual details following the clip's mental replay at each timepoint. Both BCS and NC rated

lower recall of story content after 7d compared to their immediate recall ratings [$F(1,81) = 302.818$, $p < .001$, $\eta p^2 = .789$]. No significant main effect of Group [$F(1,81) = 2.520$, $p = .116$, $\eta p^2 = .030$] or Time * Group interaction [$F(1,81) = .142$, $p = .707$, $\eta p^2 = .002$] were observed, suggesting similar perceived memory for general story content in both BCS and NC (Figure 3A).

Similarly, both groups rated the vividness of their recollection lower after 7d [$F(1,81) = 353.120$, $p < .001$, $\eta p^2 = .813$]. BCS endorsed lower vividness ratings relative to NC [$F(1,81) = 5.978$, $p = .017$, $\eta p^2 = .069$], indicating lower overall perceived episodic memory quality in BCS. No Time * Group interaction was observed [$F(1,81) = 2.508$, $p = .117$, $\eta p^2 = .030$] (Figure 3B).

BCS and NC groups rated similar levels of perceived cognitive workload during the film clip recall task using the NASA-TLX [$F(1,80) = 2.453$, $p = .121$, $\eta p^2 = .030$], with both groups rating higher cognitive workload scores during delayed retrieval [$F(1,80) = 43.961$, $p < .001$, $\eta p^2 = .355$]. No Time * Group interaction was observed [$F(1,80) = .945$, $p = .334$, $\eta p^2 = .012$] (Figure 3C).

Figure 3. *Story content and perceptual vividness memory ratings, and subjective cognitive workload.* (A) Story content ratings, (B) perceptual vividness ratings, and (C) cognitive workload for non-cancer controls (white bars) and breast cancer survivors (grey bars). Individual data points for each group are presented in light grey. Error bars represent the standard error of the mean (SEM). Abbreviations: BCS, breast cancer survivors; DR, delayed recall; IR, immediate recall; NC, non-cancer control. * denotes $p < .05$, *** denotes $p < .001$.



3.2 Forgotten Clips

A time-dependent increase in forgetting of clips was observed [$F(1,81) = 396.527$, $p < .001$, $\eta p^2 = .830$], and the number of forgotten clips did not differ between BCS and NC Groups [$F(1,81) = 1.781$, $p = .186$, $\eta p^2 = .022$]. No Time * Group interaction [$F(1,81) = .649$, $p = .423$, $\eta p^2 = .008$] was observed, suggesting comparable rates of overall forgetting over time (Figure 4A).

3.3 Central Details

Breast cancer survivors recalled fewer central details than NC [$F(1,81) = 4.322$, $p = .041$, $\eta p^2 = .051$]; however, this did not remain significant following Bonferroni correction for multiple comparisons (p adj = .01). A main effect of Time was evident, with both groups reporting fewer details at delayed retrieval [$F(1,81) = 178.689$, $p < .001$, $\eta p^2 = .688$]. The lack of Time * Group interaction [$F(1,81) = .262$, $p = .610$, $\eta p^2 = .003$] indicates that this decline followed a similar pattern in both groups (Figure 4B).

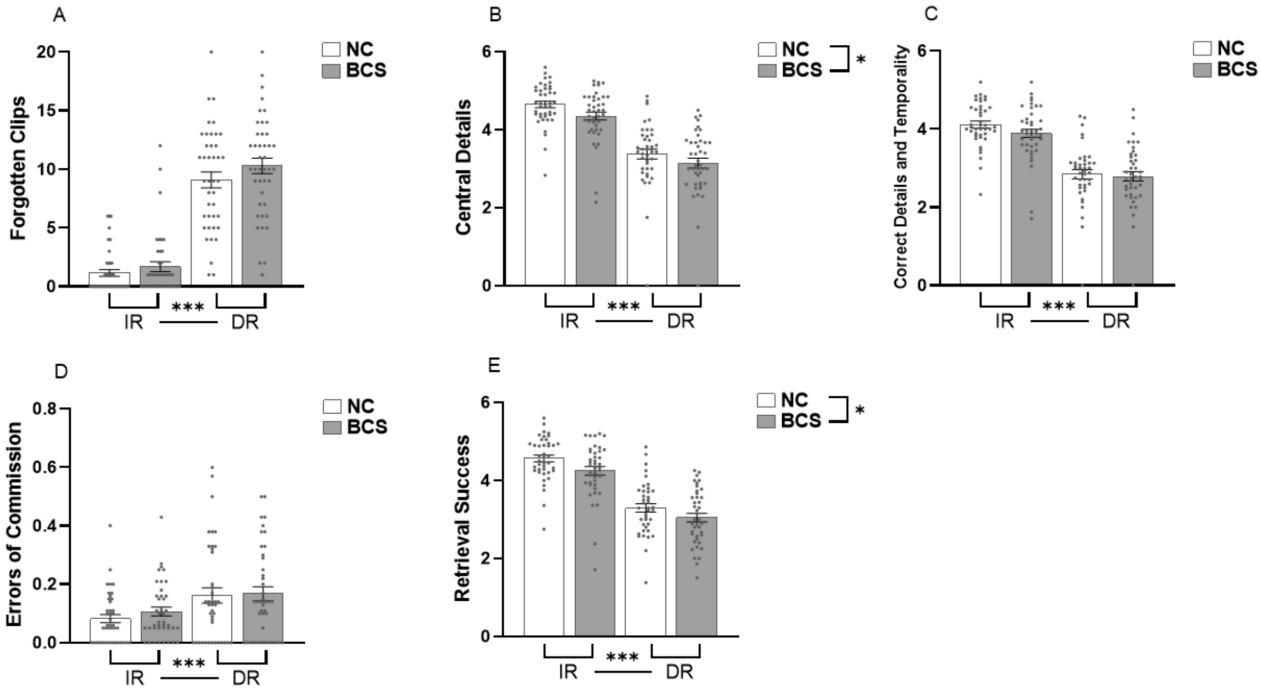
Exploratory analyses were conducted to assess the impact of cancer treatment on temporal sequencing of memories. No group differences in temporal accuracy of central elements emerged [$F(1,81) = 1.416$, $p = .238$, $\eta p^2 = .017$]. Temporal accuracy declined significantly over Time [$F(1,81) = 162.007$, $p < .001$, $\eta p^2 = .667$], and comparably across Time * Group [$F(1,81) = 1.117$, $p = .294$, $\eta p^2 = .014$] (Figure 4C).

More commission errors were made over Time [$F(1,81) = 12.192$, $p = .001$, $\eta p^2 = .131$], reflecting a general rise in false recollections after 7d. Commission errors did not differ between Groups [$F(1,81) = .436$, $p = .511$, $\eta p^2 = .005$], and no Time * Group interaction was observed [$F(1,81) = .190$, $p = .664$, $\eta p^2 = .002$] (Figure 4D).

To assess retrieval success of central details, commission errors were subtracted from the correct central detail score for each clip. BCS had lower overall retrieval success than NC [$F(1,81) = 4.622$, $p = .035$, $\eta p^2 = .054$]; though this did not survive Bonferroni correction (p adj = .01). A significant decline in retrieval success was observed over Time [$F(1,81) = 175.831$, $p <$

.001, ηp^2 = .685], but no Time * Group interaction [$F(1,81)$ = .321, p = .573, ηp^2 = .004] was observed (Figure 4E).

Figure 4. *Forgotten clips and central detail retrieval at immediate and delayed time points.* (A) Number of forgotten clips, (B) correct central details, (C) correct central details and temporal sequence, and (D) errors of commission, (E) central detail retrieval success recalled by breast cancer survivors (grey bars) and non-cancer controls (white bars). Individual data points for each group are presented in light grey. Error bars represent the SEM. Abbreviations: BCS, breast cancer survivors; DR, delayed recall; IR, immediate recall; NC, non-cancer control. * denotes p < .05, *** denotes p < .001.



3.4 Peripheral Details

BCS reported fewer peripheral details than NC [$F(1,81)$ = 7.494, p = .008, ηp^2 = .085]. A decline in peripheral detail recall over Time [$F(1,81)$ = 264.779, p < .001, ηp^2 = .766] occurred in both groups. The significant Time * Group interaction [$F(1,81)$ = 6.633, p = .012, ηp^2 = .076] indicated that BCS reported fewer peripheral details than NC during the immediate recall session (p = .003) and both BCS and NC reported fewer peripheral details across time (p < .001 for both) (Figure 5A).

Commission errors increased over Time [$F(1,81) = 4.947$, $p = .029$, $\eta p^2 = .059$], and there was a main effect of Group [$F(1,81) = 5.943$, $p = .017$, $\eta p^2 = .070$]; however, this was no longer significant after applying Bonferroni correction (p adj = .016). A significant Time * Group interaction [$F(1,81) = 6.567$, $p = .012$, $\eta p^2 = .077$] was observed. The two groups did not differ in memory distortions at immediate recall ($p = .226$). However, by the delayed recall session, NC produced more errors than BCS ($p = .004$), and showed a greater increase in errors over time ($p = .001$) (Figure 5B).

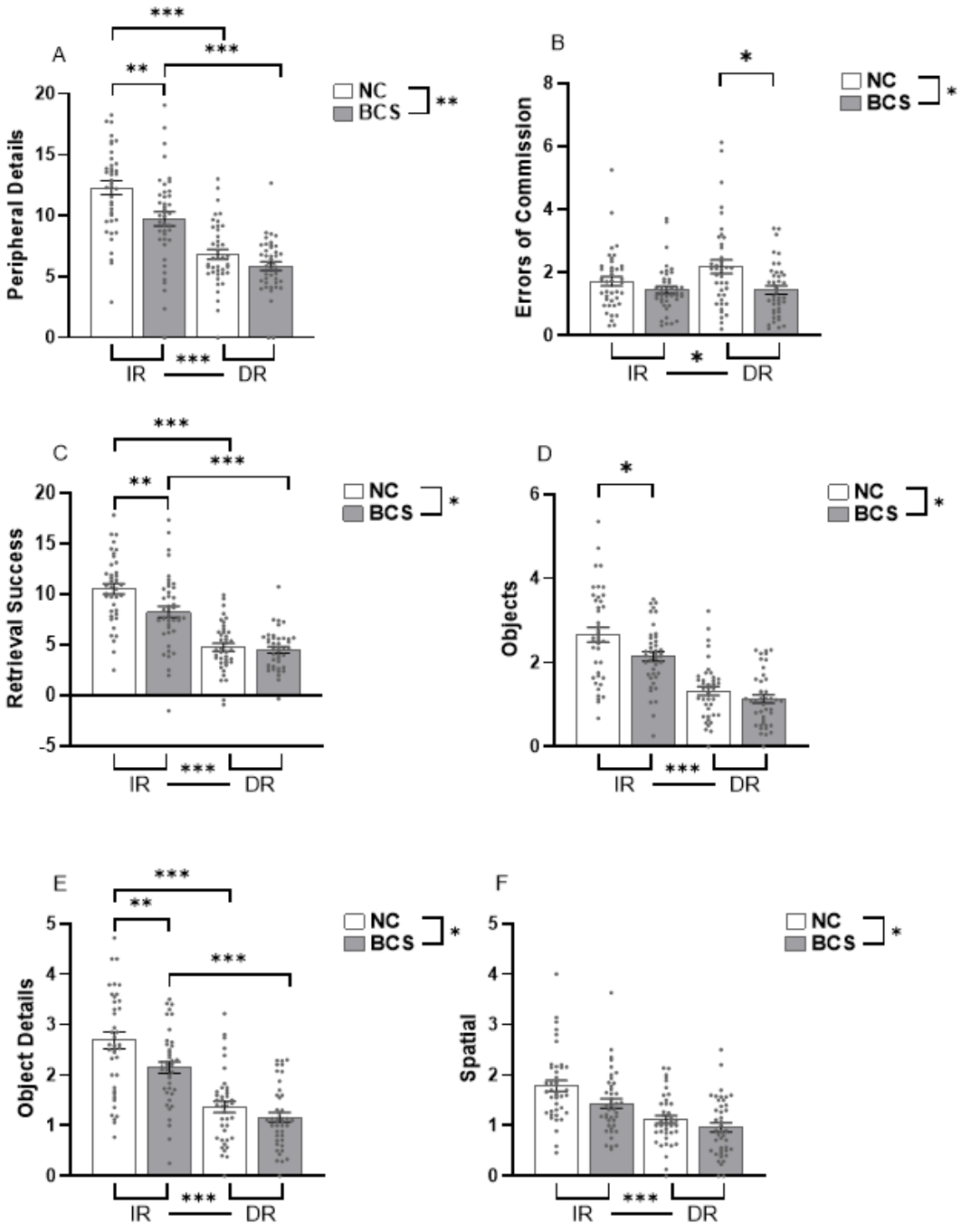
To account for the rate of errors, we evaluated retrieval success for peripheral details. Commission errors were subtracted from the correct peripheral detail score for each clip. Following this correction, BCS had lower overall retrieval success than NC [$F(1,81) = 4.674$, $p = .034$, $\eta p^2 = .055$], but again this did not survive Bonferroni correction (p adj = .016). Both groups had a time-dependent reduction of retrieval success [$F(1,81) = 244.761$, $p < .001$, $\eta p^2 = .751$]. Notably, a significant Time * Group interaction emerged [$F(1,81) = 9.601$, $p = .003$, $\eta p^2 = .106$] with NC demonstrating a higher retrieval success than BCS at immediate recall ($p = .005$), whereas their performance did not differ at delayed recall ($p = .623$; Figure 5C).

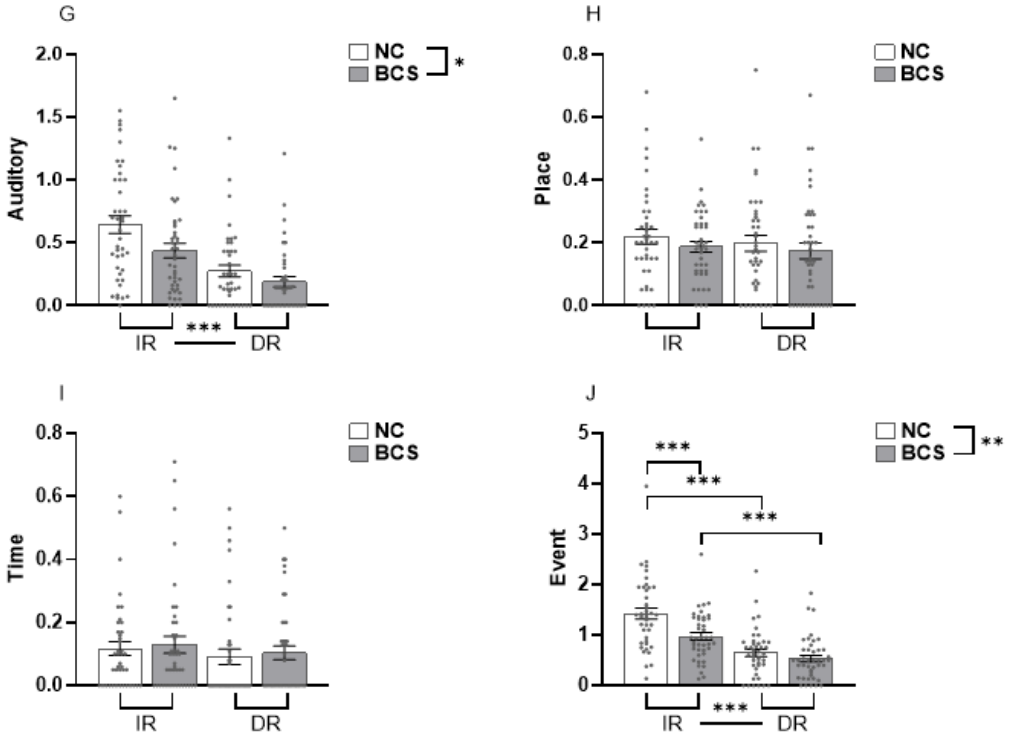
To better understand the specific types of peripheral details that are sensitive to chemotherapy-related memory dysfunction, we conducted exploratory analyses examining peripheral detail subtypes including object and object details, spatial, auditory, place, time, and event-related details (see Table 1 for full statistical results). Although both groups recalled fewer objects, object detail, spatial, auditory, and event-related details over time, BCS reported fewer details compared to NC (all p's < .050), these group effects did not survive Bonferroni correction (p adj = .007; Figures 5D-J and Table 1).

Table 3. *RM ANOVA statistical results for peripheral detail sub-types. Between-subject results for Group (breast cancer survivors and non-cancer controls).* Within-subject results for Time (immediate and delayed recall) and Time * Group interactions. * denotes *p* adj < .007, following Bonferroni correction.

Variables	df	F	p	Partial n^2
Object				
Time	1,81	232.28	<.001*	.74
Group	1,81	4.88	.03	.05
Time*Group	1,81	1.03	.04	.04
Object details				
Time	1,81	102.35	<.001*	.55
Group	1,81	2.81	.09	.03
Time*Group	1,81	.06	.42	.008
Spatial details				
Time	1,81	74.52	<.001*	.47
Group	1,81	4.27	.04	.05
Time*Group	1,81	1.79	.18	.02
Auditory details				
Time	1,81	62.03	<.001*	.43
Group	1,81	4.66	.03	.05
Time*Group	1,81	2.84	.09	.03
Place				
Time	1,81	.82	.36	.01
Group	1,81	1.29	.25	.01
Time*Group	1,81	.01	.91	.000
Time				
Time	1,81	2.68	.11	.03
Group	1,81	.11	.73	.001
Time*Group	1,81	.02	.86	.000
Event				
Time	1,81	126.06	<.001*	.61
Group	1,81	8.44	.005	.09
Time*Group	1,81	9.07	.003	.11

Figure 5. *Peripheral detail retrieval at immediate and delayed time points*. (A) Peripheral details, (B) errors of commission, (C) retrieval success, (D) object, (E) object details, (F) spatial, (G) auditory, (H) place, (I) time, and (J) event details recalled by breast cancer survivors (grey bars) and non-cancer controls (white bars). Individual data points for each group are presented in light grey. Error bars represent the SEM. Abbreviations: BCS, breast cancer survivors; DR, delayed recall; IR, immediate recall; NC, non-cancer control. * denotes $p < .05$, ** denotes $p < .01$, *** denotes $p < .001$.





4. Discussion

This study is the first to investigate the effects of chemotherapy treatment on complex episodic memory using ecologically valid, naturalistic stimuli. The film clip stimuli closely replicate the dynamic, multimodal nature of real-life event experiences, engaging episodic memory, spatial-temporal integration, and contextual processing (Bailey & Smith, 2024; Chen et al., 2016, 2017; Ezzyat & Davachi, 2011; Fenerci et al., 2025; Lee et al., 2020; Penaud et al., 2023). These functions are closely tied to hippocampal processing, and enable a rich, multi-modal evaluation of memory performance. Importantly, this study systematically classified the events' content into its central components, capturing the gist-like and schematic elements of an event, and into its peripheral components that characterize perceptually rich, context-specific, episodic re-living of a unique event. Given the known susceptibility of the hippocampus to the neurotoxic effects of chemotherapy (Ahles et al., 2002; Ahles & Root, 2018; Sekeres et al., 2021; Winocur et al., 2018b), we predicted that these peripheral and temporal elements would be especially sensitive to impairment in breast cancer survivors due to their reliance on hippocampal processing for both encoding and retrieval.

4.1 Reduced Subjective Vividness with Preserved Narrative Recall in Breast Cancer Survivors

Breast cancer survivors reported experiencing less perceptually vivid recollection of the film clip events compared with non-cancer controls, while their perceived recall of the central storyline was comparable between groups. This dissociation suggests that survivors primarily experience reductions in the perceptual and contextual richness and vividness of their memories rather than in their perceived ability to remember the overall narrative structure of events.

4.2 Impaired Encoding of Peripheral Details with Attenuated Forgetting Over Time

Breast cancer survivors recalled significantly fewer peripheral details than controls at immediate retrieval. These findings suggest that early stages of event memory, particularly encoding and initial retrieval, are especially sensitive to treatment-related impairment. This pattern is consistent with findings from other populations with medial temporal lobe-related episodic memory deficits (Gilboa et al., 2006; Rosenbaum et al., 2005; Steinvorth et al., 2005; St-Laurent et al., 2009). By the 7-day delay, group differences in peripheral recall were no longer evident. Both groups showed the expected decline in peripheral details over time, reflecting a reduced reliance on hippocampal processes and increasing support from extra-hippocampal regions such as the medial prefrontal cortex. This pattern aligns with models of memory transformation, whereby initially detailed, hippocampal-dependent memories become more gist-like and schematic as they are consolidated across distributed neocortical networks (Bonasia et al., 2018; Sekeres et al., 2018, 2024; Tarder-Stoll et al., 2026; Winocur & Moscovitch, 2011). In line with this interpretation, low peripheral recall observed in BCS at the immediate timepoint likely reflects weaker encoding rather than retrieval failure, leaving fewer details available for later recall. Rather than reflecting greater time-dependent forgetting in controls, this pattern likely reflects a floor effect, where lower initial encoding and immediate recall of peripheral details in survivors leaves less room for decline, while the higher baseline recall in controls allows for greater natural forgetting over time.

Retrieval of perceptually-detailed episodic elements primarily engages posterior hippocampus, while generalized, gist-like recall of an event engages more anterior regions of the hippocampus (Moser & Moser, 1998; Poppenk et al., 2013; Poppenk & Moscovitch, 2011). While structural and functional evidence of chemotherapy-related effects along the hippocampal long-axis remains limited, reduced posterior hippocampal volume predicted impoverished episodic autobiographical memory in 18-month remitted BSC (Bergouignan et al., 2011), supporting the link between impoverished episodically detailed event memories and posterior hippocampal integrity. Additionally, altered resting-state functional connectivity in both anterior and posterior hippocampal regions has been observed (Feng et al., 2020), suggesting intrinsic network disruptions throughout the hippocampus.

Although breast cancer survivors recalled fewer peripheral details overall than non-cancer controls, there were no significant group differences for any individual peripheral detail subtype. These findings differed from our expectations. Previous research reported reduced recall of object and object-specific details in cancer survivors, consistent with neuroimaging evidence showing reduced activation and gray matter density in the fusiform cortex following chemotherapy (Li et al., 2018; Pergolizzi et al., 2019). Similarly, poorer recall of spatial details has been associated with chemotherapy-related alterations in parahippocampal function (de Ruiter et al., 2011; Scherling et al., 2011), a region critical for representing environmental context and spatial layouts (Aminoff et al., 2013; Bohbot et al., 1998). We also anticipated reduced recall of auditory details based on evidence that certain chemotherapy agents, particularly platinum-based compounds such as cisplatin and carboplatin, can cause ototoxicity and hearing loss in up to 60% of patients (Chattaraj et al., 2023; Dillard et al., 2022). Rather than directly impairing memory for auditory information, chemotherapy-related hearing deficits may interfere with perception and encoding of auditory information, increase cognitive effort during task performance, and reduce subsequent episodic memory recall (Pichora-Fuller et al., 2016).

Several factors may explain why these differences were not observed. The study may have had limited statistical power to detect differences within individual peripheral detail

categories. For example, the film clips contained relatively few auditory details, reducing sensitivity to detect group differences in recall of this subtype. Additionally, ototoxic effects are most commonly associated with platinum-based chemotherapy agents (Chattaraj et al., 2023; Dillard et al., 2022), and therefore, variability in treatment type, which was not available for this study, may have obscured potential differences in the recall of auditory details.

4.3 Preserved Gist-Like Recall of Central Event Details

Consistent with our hypothesis, breast cancer survivors demonstrated relatively preserved recall of central (gist-based) details, performing similarly to non-cancer controls at both immediate and delayed retrieval. Although there was a trend toward reduced recall of central details among survivors, this difference did not remain significant following adjustment for multiple comparisons. Therefore, the present findings provide stronger evidence for impairments in the recall of peripheral, context-rich details than for deficits in gist-based memory. This pattern is consistent with previous research demonstrating that individuals with medial temporal lobe dysfunction show disproportionate difficulties recalling detailed episodic information while retaining access to the central or schematic aspects of events (Gilboa et al., 2006; Rosenbaum et al., 2005; Steinvorth et al., 2005; St-Laurent et al., 2009).

4.4 Preserved Temporal Sequencing of Central Events

Exploratory analyses indicated that breast cancer survivors demonstrated temporal sequencing of events comparable to that of controls, suggesting that the temporal organization of central event memory is not detrimentally impacted by chemotherapy treatment, despite this process' reliance on the hippocampus for temporal sequencing (Eichenbaum, 2014; Kraus et al., 2013). Consistent with other peripheral detail sub-types, temporal sequencing accuracy declined similarly in both groups across the 7-day delay, reflecting the normal transformation of episodic memories over time, as complex event memories become more gist-based.

These findings were contrary to our hypothesis that chemotherapy treated breast cancer survivors would exhibit impaired temporal sequencing due to treatment-related hippocampal neurotoxicity (Reddy et al., 2021). Although survivors tended to recall fewer accurate temporal

details than controls, this difference was not statistically significant, suggesting that any treatment-related impairment is likely subtle and less severe than the deficits observed following traumatic brain injury (Dulas et al., 2022) or bilateral hippocampal damage associated with amnesia (Evans et al., 2024). One possible explanation is that participants reconstructed the temporal order of central events using semantic knowledge of how everyday situations typically unfold, reducing reliance on hippocampal-dependent episodic retrieval (Ding & Zacks, 2026). In contrast, accurately sequencing peripheral details may depend more on richly detailed episodic memory representations and therefore be more sensitive to treatment-related impairment (Lehn et al., 2009). However, the dynamic nature of the film-based free recall task limited our ability to reliably score peripheral temporal sequencing, preventing us from testing this hypothesis.

4.5 Limitations

One limitation of the present study is that, although the groups were generally well matched on demographic characteristics, a greater proportion of breast cancer survivors were post-menopausal. This is common in this patient population, as cancer treatments may induce premature menopause (Rosenberg & Partridge, 2013). Menopause has been independently associated with poorer episodic memory performance (LaPlume et al., 2024; Rentz et al., 2017) and increased subjective memory complaints (Naysmith et al., 2026), making it is difficult to disentangle the contributions of menopausal status and cancer-related factors to the observed cognitive differences. Additionally, the cross-sectional design precludes conclusions about the temporal trajectory of cognitive changes following treatment. Future longitudinal studies incorporating detailed treatment characteristics (e.g., chemotherapy regimen, cumulative dose, endocrine therapy) are needed to better characterize dose-dependent treatment effects and to determine how individual factors, including age, menopausal status, and cognitive reserve, moderate cognitive outcomes (Sekeres et al., 2021; Wefel & Schagen, 2012).

5. Conclusion

Together, these results indicate that chemotherapy may reduce the overall richness of event representations, while preserving more central, schematic, representations of episodic memories. Cancer survivors showed preserved temporal organization of events, suggesting that the structural framework of event memories remains intact. Naturalistic memory paradigms that capture the qualitative features of event memory may provide a sensitive approach for detecting treatment-related cognitive changes.

6. References

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CHAPTER 6

Discussion

1. Summary of Findings

Historically, breast cancer survivorship research and care have been shaped by the assumption that patients would return to pre-illness levels of functioning following completion of treatment, an expectation that is increasingly challenged by evidence of persistent long-term physical, psychological, and cognitive effects (Pinto & de Azambuja, 2011; Ross et al., 2022). Therefore, the present study aimed to better understand the long-term consequences of breast cancer treatment, with a particular focus on episodic memory functioning and mental health outcomes.

Several key findings emerged across this thesis. First, the literature review identified a critical gap in the cancer survivorship literature. Despite substantial evidence that chemotherapy-related neurotoxicity affects hippocampal structure and function, relatively little research has examined episodic memory using complex, naturalistic tasks that more closely reflect the demands of everyday remembering. Consequently, the extent to which treatment-related cognitive difficulties affect real-world memory functioning remains poorly understood.

Second, the empirical findings demonstrated that breast cancer survivors experience significantly greater psychological and physiological distress than non-cancer controls. Survivors reported higher levels of stress, anxiety, depression, fatigue, and sleep disturbance, and these factors were strongly interrelated, suggesting that difficulties across multiple domains may accumulate and contribute to ongoing challenges in survivorship.

Third, this thesis revealed important differences between traditional neuropsychological assessments and more naturalistic measures of memory. Although breast cancer survivors performed comparably to controls on a standardized verbal paired associates task, they demonstrated poorer performance on narrative-based memory tasks and reported greater cognitive workload during this task. These findings suggest that conventional neuropsychological tests may underestimate the cognitive challenges experienced by survivors in everyday life and

highlight the importance of incorporating ecologically valid measures and measures of cognitive effort.

Finally, the use of ecologically valid memory assessments revealed evidence of episodic memory difficulties in breast cancer survivors. Survivors recalled significantly fewer peripheral (contextual) details of events than controls, including object, spatial, auditory, and event-specific information. Although survivors also tended to recall fewer central (gist-based) details, this difference was no longer significant following Bonferroni correction. While the rate of forgetting over time was similar across groups, survivors consistently encoded and retrieved fewer details overall, indicating a persistent reduction in episodic memory performance rather than accelerated forgetting.

Taken together, the findings of this thesis provide novel evidence that breast cancer survivors experience enduring difficulties that extend beyond treatment completion and are not always detectable using well-validated standard neuropsychological assessments. By integrating ecologically valid and robust laboratory-based measures of memory, this work offers a more comprehensive characterization of cancer-related cognitive impairment and identifies specific episodic memory processes that may be particularly vulnerable to treatment-related effects. Beyond cognitive functioning, this work also highlights the enduring psychological and physiological consequences of cancer treatment and demonstrates how impairments across multiple mental health domains may interact to contribute to persistent emotional difficulties long after treatment completion. Collectively, these findings advance current approaches to assessing cognitive outcomes in cancer survivorship and support the integration of ecologically valid measures, in addition to standardized laboratory measures, into both research and clinical practice.

2. Mental Health

Although numerous studies have examined the impact of cancer treatment on mental health functioning among breast cancer survivors, as well as the relationships between these variables

(Bower et al., 2006; Breidenbach et al., 2022; Fortner et al., 2002; Jones et al., 2015; Lopes et al., 2022; Lowery-Allison et al., 2018), the present study extends the existing literature by assessing a broader range of commonly affected psychosocial outcomes in this population up to 20 years post-treatment compared to non-cancer controls. In doing so, our findings further emphasize the multifaceted and enduring nature of mental health difficulties experienced by many breast cancer survivors. Importantly, these concerns—including sleep disturbances, stress, anxiety, depression, and fatigue—were also found to be interrelated in this study. For example, individuals experiencing elevated anxiety and depressive symptoms frequently also reported sleep disturbances (Bower, 2008). These findings suggests that intervention targeting one or more domains may also produce indirect benefits in other areas of functioning. For instance, psychological intervention aimed at reducing anxious thoughts that interfere with sleep onset may improve sleep quality, while interventions targeting sleep disturbances may also help alleviate mental health challenges (Howarth & Miller, 2024; Hyndych et al., 2025). Given the bidirectional relationships among these mental health factors, a more comprehensive understanding of their complex interactions is essential. Taken together, these findings highlight the importance of ongoing comprehensive psychological assessment within cancer survivorship care, which may ultimately support more targeted and effective treatment planning.

3. Episodic Memory

To our knowledge, this is the first study to examine long-term episodic memory functioning in breast cancer survivors using multiple naturalistic memory paradigms designed to capture the complexity of everyday remembering. Previous research investigating cancer-related cognitive impairment has relied predominantly on traditional neuropsychological assessments, including list-learning, story recall, and verbal paired associate tasks (Gaynor et al., 2022; Koppelmans et al., 2012; Root et al., 2016). Although these measures are reliable and well validated, they do not reflect the cognitive demands of real-world remembering (Serino & Repetto, 2018; Spooner & Pachana, 2006). Consequently, subtle but meaningful memory difficulties may remain undetected despite survivors reporting ongoing cognitive concerns. The present study addresses

this gap by incorporating ecologically valid memory measures with detailed scoring procedures that capture both quantitative and qualitative aspects of episodic recall.

Breast cancer survivors recalled significantly fewer peripheral details than non-cancer controls at immediate retrieval, suggesting early episodic processes such as encoding and initial retrieval are particularly vulnerable to treatment-related effects. This pattern aligns with evidence from populations with medial temporal lobe dysfunction, who similarly demonstrate difficulties retrieving richly contextualized episodic information (Gilboa et al., 2006; Phillips et al., 2024; Rosenbaum et al., 2005; Steinvorth et al., 2005; St-Laurent et al., 2009, 2014). However, at the 7-day delay, group differences in peripheral recall were no longer evident, with both groups showing similar declines over time. This aligns with models of memory transformation, in which detailed, hippocampus-dependent representations become more schematic as consolidation shifts reliance toward distributed neocortical networks, including medial prefrontal regions (Bonasia et al., 2018; Sekeres et al., 2024; Sekeres, Winocur, & Moscovitch, 2018; Tarder-Stoll et al., 2025; Winocur & Moscovitch, 2011). Within this framework, poorer immediate peripheral recall in survivors likely reflects weaker encoding rather than retrieval failure, with the absence of delayed group differences possibly reflecting a floor effect. Although breast cancer survivors tended to recall fewer central (gist-based) details than non-cancer controls, this difference was no longer significant following Bonferroni correction. As such, gist-based memory appeared to be relatively preserved compared to the more pronounced impairments observed for peripheral, context-rich details. This pattern is consistent with findings from individuals with medial temporal lobe damage, in whom schematic or gist-based aspects of memory are often better preserved than detailed episodic recollection (Gilboa et al., 2006; Rosenbaum et al., 2005; Steinvorth et al., 2005; St-Laurent et al., 2009).

On the narrative memory task, breast cancer survivors also recalled fewer verbatim and gist-based details compared to controls. Despite these differences, both groups performed similarly across immediate and delayed recall, suggesting similar patterns of forgetting even over a brief period of 20 minutes. These findings are noteworthy given that verbatim memory typically

declines over time, even in healthy individuals (Reyna et al., 2016). Consistent with prior work (Taler et al., 2021), both groups showed reductions in verbatim details following a delay, while gist recall increased, reflecting the typical shift toward more schematic representations over time (Sekeres, Winocur, & Moscovitch, 2018). An unexpected finding was survivors reporting fewer gist details than non-cancer controls, potentially indicating generally less accessible memory content (Sekeres et al., 2016). Interestingly, only non-cancer controls had a significant increase in memory distortions over time. Rather than reflecting superior memory accuracy, the lower distortion and gist scores among breast cancer survivors likely indicate impairments in memory encoding (Gaynor et al., 2022; Root et al., 2016). While memory naturally transforms over time, becoming less specific and more prone to distortion particularly for schema-consistent events, breast cancer survivors may encode fewer details from the outset, leaving less information available for later recall or distortion (Gilboa & Moscovitch, 2021; Sekeres, Winocur, & Moscovitch, 2018; Tarder-Stoll et al., 2025). This interpretation is reinforced by lower overall recall and supported by retrieval success scores, which account for both accuracy and completeness of memory.

In contrast to the findings obtained from the narrative and film-based tasks, breast cancer survivors performed similarly to controls on the verbal paired associates task. This pattern is noteworthy because it suggests that some forms of associative learning may remain relatively preserved following treatment. More importantly, it highlights a discrepancy between traditional laboratory-based measures and more complex memory paradigms. In contrast to previous findings, survivors did not show the expected learning curve across trials and instead performed at a comparable level to controls from the outset and across trials, a pattern that also diverges from typical performance in healthy populations, where gradual improvement across trials is usually observed (Gaynor et al., 2022; Quesnel et al., 2009; Root et al., 2016). Nonetheless, they are consistent with prior literature indicating that standard verbal paired associate tasks may lack sensitivity for detecting subtle cognitive deficits, even in populations with known memory impairment such as individuals with mild cognitive impairment (Pike et al., 2013). Consequently,

well validated and robust standard laboratory-based memory tasks may underestimate the subtle cognitive difficulties experienced by breast cancer survivors in real-world settings.

Although conceptually distinct, the verbatim details assessed in the narrative task and the peripheral details assessed in the film clip task reflect overlapping aspects of episodically rich recollection. The present findings demonstrate that breast cancer survivors showed impairments in both types of detailed memory relative to non-cancer controls, suggesting broader difficulties with the retrieval of richly contextualized episodic information. Importantly, different aspects of episodic recollection appear to rely on distinct regions along the hippocampal long axis. Generalized or gist-like recall engages, to some extent, more anterior hippocampal regions, whereas the retrieval of perceptually rich and detailed episodic information relies more heavily on the posterior hippocampus (Moser & Moser, 1998; Poppenk et al., 2013; Poppenk & Moscovitch, 2011). Although evidence examining chemotherapy-related alterations along the hippocampal long axis remains limited, reduced posterior hippocampal volume has been associated with impoverished episodic autobiographical memory in breast cancer survivors 18 months following remission (Bergouignan et al., 2011), further supporting a link between posterior hippocampal integrity and the retrieval of richly detailed episodic memories.

Overall, the findings suggest that cancer-related cognitive impairment may be characterized less by accelerated forgetting and more by reduced access to rich episodic representations of events. Importantly, these difficulties were apparent following both brief (20-minute) and extended (7-day) delays and were most consistently detected using memory measures that more closely approximated everyday remembering. Collectively, these findings highlight important limitations of relying solely on conventional neuropsychological assessments and underscore the value of incorporating naturalistic memory measures into both cancer survivorship research and clinical practice.

4. Discrepancies Between Subjective and Objective Cognitive Measures

Our findings demonstrate that breast cancer survivors experienced difficulties on ecologically valid episodic memory tasks and reported greater subjective cognitive difficulties. Although objective memory performance was associated with subjective cognitive concerns in the present study, this relationship has not been consistently observed in the broader literature (Hutchinson et al., 2012; O'Farrell et al., 2017; Onyedibe et al., 2025). Consequently, it is important to consider the multiple interacting factors that may contribute to the relationship between objective and subjective cognitive functioning, including mental health, cognitive reserve, premorbid intellectual functioning, and compensatory cognitive effort (Ahles & Hurria, 2018).

Our findings demonstrate that breast cancer survivors reported greater subjective cognitive difficulties than non-cancer controls, with particular difficulties in episodic and semantic memory, as well as heightened perceived difficulty in recalling peripheral event details. Although subjective cognitive concerns were associated with objective memory performance in the present study, this relationship is not consistently observed in the broader literature (Hutchinson et al., 2012; O'Farrell et al., 2017; Onyedibe et al., 2025). Indeed, subjective cognitive complaints are often more strongly associated with symptoms of anxiety, depression, fatigue, and psychological distress than with objective neuropsychological impairment (Oliva et al., 2024; Onyedibe et al., 2025). Rather than suggesting that subjective concerns are inaccurate or solely psychological in nature, these findings highlight the multifaceted nature of cognitive complaints. Subjective cognitive difficulties likely reflect the combined influence of cognitive, emotional, and physiological experiences that shape day-to-day functioning in cancer survivorship.

An important contribution of the present study is the finding that breast cancer survivors reported significantly greater cognitive workload while completing memory tasks than non-cancer controls. This finding suggests that cognitive performance and cognitive effort are not synonymous. Even when survivors achieve levels of objective performance comparable to healthy individuals, they may require substantially greater mental effort to do so. As a result, equivalent performance should not necessarily be interpreted as evidence of intact cognitive

functioning. This interpretation is consistent with neuroimaging research demonstrating structural and functional brain changes following chemotherapy, including hippocampal neurotoxicity, reduced grey and white matter integrity, alterations in default mode network functioning, and increased activation within frontal regions during cognitive tasks (Kesler et al., 2013; McDonald et al., 2010; Menning et al., 2017). Such hyperactivation has often been interpreted as evidence of compensatory neural recruitment, whereby survivors engage additional neural resources to maintain cognitive performance (Ansari & Derakshan, 2011). Supporting this interpretation, increased hippocampal-precuneus connectivity has been associated with greater subjective cognitive concerns among chemotherapy-treated patients, suggesting that alterations within memory-related networks may reflect attempts to compensate for subtle cognitive inefficiencies (Apple et al., 2018). Importantly, increased cognitive effort may have meaningful real-world consequences even when objective performance appears relatively preserved. Everyday activities such as managing appointments, maintaining employment, or engaging in social interactions often require sustained cognitive effort over extended periods. If survivors must consistently expend greater cognitive resources to achieve the same level of performance, they may be more vulnerable to cognitive fatigue and may experience greater difficulty meeting daily and occupational demands. Consequently, cognitive workload may represent an important but often overlooked dimension of cancer-related cognitive impairment.

The present findings also highlight the importance of considering individual baseline functioning when evaluating cognitive outcomes. Among the various factors that can influence cognitive functioning, cognitive reserve is an important protective against cognitive decline (Ahles et al., 2010; Liesto et al., 2022). Furthermore, survivors with strong premorbid intellectual functioning may continue to perform within normative ranges following treatment while nevertheless experiencing notable declines relative to their own baseline functioning, which has been observed in other clinical populations, such as Multiple Sclerosis (Stein et al., 2024). This possibility underscores the value of obtaining pre-treatment cognitive assessments whenever feasible, as changes relative to an individual's baseline may be more informative than comparisons to population norms alone.

Overall, the findings of this thesis suggest that subjective and objective cognitive measures should not be viewed as competing sources of information, but rather as complementary indicators of cognitive functioning. Survivors' subjective experiences, objective performance, cognitive workload, psychological well-being, and functional outcomes each provide unique insight into the impact of cancer treatment on daily life. Integrating these perspectives may improve the identification, characterization, and management of cancer-related cognitive difficulties and ultimately support more responsive and person-centred survivorship care.

5. Factors Contributing to Cognitive and Mental Health Difficulties

An important consideration when interpreting the present findings is the substantial heterogeneity that characterizes breast cancer survivorship. Not all survivors experience cognitive or psychological difficulties following treatment, and among those who do, the severity, duration, and nature of symptoms vary considerably. This variability suggests that cancer-related cognitive and psychological difficulties cannot be attributed to a single cause. Rather, they are likely shaped by the complex interaction of biological, psychological, and social factors that influence both vulnerability and resilience throughout the cancer trajectory. Consequently, a biopsychosocial framework provides a useful lens through which to understand the findings of the present study.

With respect to psychological functioning, previous research has identified numerous factors associated with increased risk for persistent distress following cancer treatment, including younger age, pre-existing mental health difficulties, employment demands, caregiving responsibilities, disease characteristics, limited social support, and financial stressors (Tang et al., 2024; Tao et al., 2024). It is also important to consider the broader context in which many participants experienced cancer treatment. Recruitment for the present study occurred during and following the COVID-19 pandemic, and many survivors described treatment experiences that were shaped by pandemic-related restrictions. Social isolation, reduced access to support networks, disruptions to healthcare services, and heightened uncertainty have all been associated with poorer psychological outcomes among cancer patients (Bartmann et al., 2021;

Farewell et al., 2023; Tsui et al., 2023). Although these factors were not directly assessed in the present study, they may have contributed to the elevated distress reported by some participants and represent an important contextual consideration when interpreting the findings. Altogether, these factors may increase vulnerability to chronic stress, anxiety, depression, fatigue, and sleep disturbances, all of which were elevated among survivors in the present study. Importantly, the current findings demonstrated strong relationships among these mental health variables, suggesting that difficulties in one domain may contribute to or exacerbate difficulties in another. For example, anxiety may interfere with sleep, poor sleep may worsen fatigue, and fatigue may further contribute to emotional distress, creating self-reinforcing cycles that persist long after treatment completion.

Similarly, cognitive outcomes following breast cancer treatment are likely influenced by multiple interacting factors rather than treatment exposure alone. Biological contributors include disease characteristics, treatment type and intensity, neurotoxicity associated with chemotherapy, hormonal changes, menopausal status, and broader health-related factors (Ahles & Hurria, 2018; Ahles & Saykin, 2007; Edelstein & Bernstein, 2014; Ramalho et al., 2017). At the same time, individual differences in cognitive reserve, premorbid intellectual functioning, genetic vulnerability, and resilience may influence the extent to which survivors experience cognitive changes following treatment (Ahles & Hurria, 2018; Edelstein & Bernstein, 2014). These factors may help explain why some survivors report substantial cognitive difficulties whereas others appear relatively unaffected.

Importantly, many of the factors associated with poorer cognitive functioning overlap with those associated with psychological distress. Fatigue, sleep disturbance, anxiety, depression, and medical comorbidities have all been linked to both subjective and objective cognitive outcomes in breast cancer survivors (Ahles & Saykin, 2007; Alhola & Polo-Kantola, 2007; Berger et al., 2012; Natalucci et al., 2021; Wefel et al., 2011). This overlap is particularly relevant in light of the present findings. Survivors not only demonstrated impairments in episodic memory, but also reported elevated levels of stress, anxiety, depression, fatigue, and sleep disturbance. This

pattern suggests that cognitive and psychological difficulties are likely to be mutually reinforcing, potentially contributing to a cyclical relationship that maintains or exacerbates both domains over time.

6. Future Directions

The findings of the present thesis highlight several important directions for future research. Future studies should aim to recruit more diverse and representative samples of breast cancer survivors. Recruitment for the present study began during the COVID-19 pandemic and was conducted online to maximize accessibility and reduce barriers for immunocompromised individuals. Although this approach facilitated recruitment from across Canada and increased geographic diversity, reliance on social media-based recruitment may have contributed to the overrepresentation of younger and predominantly Caucasian participants, thereby limiting generalizability (Benedict et al., 2019; Oudat & Bakas, 2023). Future research should prioritize recruitment strategies that engage individuals from diverse racial, ethnic, socioeconomic, and geographic backgrounds to better capture the heterogeneity of survivorship experiences.

Future studies should also continue to evaluate and refine remote cognitive assessment methods. Online assessment offers several advantages, including standardized administration, increased accessibility, reduced participant burden, and the opportunity to recruit geographically diverse samples (Staffaroni et al., 2020; Tsoy et al., 2021). However, remote testing may also introduce variability related to environmental distractions, fatigue, technology access, and internet connectivity (Staffaroni et al., 2020; Tsoy et al., 2021). Although these concerns were minimized in the present study through live Zoom administration by trained researchers, future work should continue to examine the reliability, validity, and ecological relevance of remote cognitive assessment approaches, particularly for evaluating subtle cognitive difficulties in cancer survivorship.

Future studies should continue to refine the assessment of psychological and physiological outcomes. Although self-report measures provide valuable insight into survivors' lived

experiences, they are inherently limited by response biases and may not fully capture symptom severity, duration, or clinical significance. Incorporating structured clinical interviews alongside standardized questionnaires would provide a more comprehensive evaluation of psychological functioning. Similarly, objective measures of sleep functioning, such as polysomnography or actigraphy, could complement self-reported sleep assessments and provide greater insight into the role of sleep disturbances in survivorship outcomes (Grutsch et al., 2011).

In addition, future research should obtain more detailed treatment and medical information. Although treatment-related factors are known to influence cognitive functioning (Sekeres et al., 2021), incomplete patient-reported treatment data prevented examination of treatment-specific effects in the present study. Collecting detailed information regarding chemotherapy regimens, radiation exposure, endocrine therapies, disease characteristics, and treatment duration would allow researchers to better understand which aspects of treatment are most strongly associated with long-term cognitive and psychological outcomes.

Future research should incorporate comparison groups that allow the effects of breast cancer and its various treatments to be more clearly distinguished. Although the present study included a heterogeneous sample of survivors who underwent surgery, chemotherapy, radiation therapy, hormonal therapy, or combinations of these treatments—reflecting the clinical diversity of this population—this variability limited our ability to isolate the effects of individual treatments on cognitive and mental health functioning. Future studies could therefore include women recently diagnosed with breast cancer who have not yet begun treatment, subgroups differentiated according to treatment exposure (e.g., surgery alone, chemotherapy, radiation therapy, or hormonal therapy), and a non-cancer control group. Comparing these groups may help determine whether cognitive and mental health difficulties are present before treatment and clarify how they may be differentially affected by specific treatment modalities.

In addition to accounting for treatment type, future research should further examine the influence of sociodemographic and health-related variables, including age, education, income, caregiving responsibilities, menopausal status, cancer stage, and time since diagnosis and

treatment. Although exploratory analyses were conducted to assess whether these factors were associated with the present findings, they were not systematically controlled for in the primary analyses. This limits the extent to which the observed differences can be attributed specifically to cancer and its treatment, as these variables may independently influence cognitive and mental health functioning. For example, younger age, caregiving responsibilities, and lower socioeconomic status have been associated with greater psychological distress (Tang et al., 2024; Tao et al., 2024; Vodermaier et al., 2014). Future studies with larger samples should therefore include these variables as covariates or examine them as potential moderators to clarify their contribution to cognitive and mental health outcomes.

Finally, although cross-sectional studies provide valuable information regarding long-term outcomes, they cannot determine whether observed differences existed prior to treatment or emerged as a consequence of treatment-related changes. Longitudinal studies that assess individuals before treatment, during treatment, and throughout survivorship would provide stronger evidence regarding the development and trajectory of cognitive, psychological, and neural changes over time. Integrating neuroimaging, cognitive assessment, and measures of psychological well-being within such designs would also help clarify how biological, psychological, and social factors interact to influence survivorship outcomes.

7. Conclusion

Historically, completion of cancer treatment has often been viewed as the end of the cancer journey and the beginning of a return to normal functioning. The findings of the present thesis challenge this assumption by demonstrating that many breast cancer survivors continue to experience enduring psychological, physiological, and cognitive difficulties long after treatment has ended. This thesis highlights the ongoing challenges survivors experience, including elevated levels of stress, anxiety, depression, fatigue, and sleep disturbance, further underscoring the interconnected nature of mental health outcomes. This thesis also advances understanding of cancer-related cognitive impairment by showing that episodic memory difficulties are more readily detected using ecologically valid and naturalistic assessments than traditional

neuropsychological measures. These cognitive differences were also associated with increased cognitive effort during task performance, suggesting that survivors may rely on greater mental resources to achieve comparable levels of performance. Taken together, these findings support a multifaceted framework to understanding of cancer survivorship and underscore the importance of comprehensive assessment approaches that integrate objective performance, subjective experience, mental health functioning, and ecologically valid measures of cognition. Ultimately, improving recognition of these persistent challenges is essential for informing person-centred survivorship care and enhancing long-term quality of life among breast cancer survivors.

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