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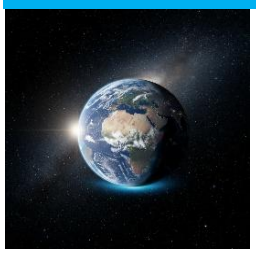

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Persistent Cognitive Dysfunction Following Systemic Chemotherapy in Women with Breast Cancer

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Abstract

Chemotherapy-related cognitive impairment (CRCI), commonly known as “chemobrain,” is a prevalent and clinically significant complication in breast cancer survivors. Cognitive deficits primarily affect memory, attention, executive function, processing speed, and verbal fluency, and may persist for months to years after treatment. CRCI arises from multiple mechanisms, including direct neurotoxicity, neuroinflammation, oxidative stress, mitochondrial dysfunction, hormonal alterations, genetic susceptibility, psychosocial stressors, and gut–brain axis changes. Neuroimaging studies demonstrate structural and functional brain alterations such as gray matter reduction, white matter microstructural changes, disrupted connectivity, and compensatory cortical hyperactivation, particularly within frontoparietal and temporal networks. Subjective cognitive complaints often correspond with objective deficits, although considerable heterogeneity exists. Precision approaches, including machine learning-based neuroimaging biotyping and multimodal cognitive assessment, enable identification of biologically distinct subgroups and improve risk stratification. Non-pharmacological interventions such as cognitive rehabilitation, physical activity, mindfulness, and psychosocial support have shown efficacy, whereas pharmacological options remain limited. Integrating biological, neuroimaging, genetic, and psychosocial data is essential for developing individualized strategies to preserve cognitive function and quality of life. Future research should prioritize longitudinal studies, biomarker discovery, ecological cognitive monitoring, and digital therapeutics to optimize precision survivorship care.

Keywords: breast cancer; chemotherapy-related cognitive impairment; chemobrain; neuroinflammation; neuroimaging; cognitive rehabilitation; precision medicine; executive function; memory deficits; survivorship care.

1. **Introduction**:

Breast cancer remains the most frequently diagnosed malignancy among women worldwide. Advances in early detection and multimodal treatment have substantially improved survival outcomes, resulting in a growing population of long-term survivors. Consequently, oncologic

priorities have shifted toward the identification and management of chronic and late treatment-related sequelae, including cognitive dysfunction.

Chemotherapy-related cognitive impairment (CRCI) has emerged as a clinically significant complication affecting memory, attention, executive functioning, and processing speed. While cognitive changes may occur during active treatment, a subset of patients experience persistent deficits months or even years after therapy completion. These impairments may adversely affect occupational functioning, social participation, and overall quality of life.

Increasing evidence suggests that CRCI is multifactorial in origin, involving complex interactions between treatment-related neurotoxicity, systemic inflammation, hormonal alterations, and individual vulnerability factors. However, the natural history, predictive markers, and mechanistic pathways underlying persistent cognitive dysfunction remain incompletely understood.

This narrative review synthesizes current evidence regarding the epidemiology, neurobiological mechanisms, neuroimaging correlates, and clinical implications of persistent cognitive dysfunction following systemic chemotherapy in women with breast cancer, with particular emphasis on emerging precision-based approaches to survivorship care.

2. Materials and Methods

This narrative review synthesizes contemporary evidence on persistent cognitive dysfunction following systemic chemotherapy in women with breast cancer. A targeted literature search was conducted using PubMed and Google Scholar. The search was performed on 20 December 2025 and focused primarily on articles published within the past five years, while seminal earlier studies were included when considered essential for contextual understanding.

Search terms included combinations of “breast cancer,” “chemotherapy-related cognitive impairment,” “cancer-related cognitive dysfunction,” “chemobrain,” “neuroimaging,” “functional MRI,” “biomarkers,” and “cognitive rehabilitation.” Only articles published in English were considered.

Clinical trials, randomized controlled trials, meta-analyses, systematic reviews, and high-quality review articles were prioritized. Studies were selected based on methodological rigor, relevance to the clinical and neurobiological aspects of CRCI, and their contribution to emerging concepts such as neuroimaging-based phenotyping and precision survivorship care.

Consistent with the narrative nature of this review, no formal systematic screening protocol, risk-of-bias assessment, or quantitative synthesis was performed.

3. Results

3.1 Global Burden of Cancer and Breast Cancer Epidemiology

Breast cancer is the most frequently diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality, posing a major public health and socioeconomic challenge in the 21st century [1]. According to GLOBOCAN 2022 estimates from the International Agency for Research on Cancer (IARC), approximately 20 million new cancer cases and 9.7 million cancer-related deaths were recorded worldwide in 2022. Within this global burden, breast cancer represents a substantial proportion of cases, ranking second in incidence and fourth in mortality worldwide [2,3]. In 2022, an estimated 2.3 million new cases of female breast cancer were diagnosed, resulting in approximately 670,000 deaths, with incidence rates increasing by 1–5% annually in nearly half of the countries evaluated [4,5]. The rising incidence underscores the urgent need for targeted early detection strategies, equitable access to treatment, and interventions addressing modifiable risk factors, particularly in low- and middle-income countries, where disparities in care persist [6].

3.2 Etiology of Breast Cancer

Breast cancer is biologically heterogeneous, encompassing distinct molecular subtypes characterized by variable clinical behavior, therapeutic response, and prognostic outcomes [6]. Its etiology is multifactorial, involving interactions between genetic susceptibility, hormonal and reproductive factors, lifestyle behaviors, and environmental exposures [6,10]. Prolonged exposure to endogenous estrogen associated with early menarche, late menopause, nulliparity, or lack of breastfeeding has been consistently linked to increased risk. High-penetrance germline mutations, particularly in BRCA1 and BRCA2, substantially elevate lifetime risk, especially among individuals with a first degree family history of the disease. Low penetrance polymorphisms in genes such as GSTM1 and NQO2 may further modify individual susceptibility. Modifiable lifestyle factors include obesity, sedentary behavior, diets high in saturated fats and refined sugars, alcohol consumption, tobacco use, and exposure to ionizing radiation [10].

3.3 Current Treatment Approaches and Role of Chemotherapy

Current management of breast cancer is increasingly personalized, guided by tumor biology, stage, and patient characteristics [8]. Standard treatment modalities include surgery, radiotherapy, systemic chemotherapy, endocrine therapy, targeted agents, and immunotherapy [6]. Chemotherapy remains a cornerstone in both early stage and high-risk or biologically aggressive disease, administered in neoadjuvant or adjuvant settings [12], most commonly using anthracycline - and taxane - based regimens. Therapeutic decisions are individualized based on tumor aggressiveness, recurrence risk, patient age, comorbidities, and overall treatment objectives [9,11]. Although targeted and immune-based therapies have expanded the therapeutic armamentarium, chemotherapy continues to play a central role in improving survival outcomes [11]. While cross - sectional studies suggest the presence of cognitive symptoms up to 20 years after treatment, longitudinal studies confirm impairments lasting up to four years following the end of chemotherapy [21]. As survival rates improve and the population of long-term breast cancer survivors grows, attention has increasingly shifted toward late and persistent adverse effects of systemic therapy [13]. CRCI represents one of the most clinically significant long-term complications, affecting memory, attention, processing speed, and executive function. Up to one-third of breast cancer survivors may experience clinically meaningful deficits following chemotherapy, with longitudinal studies showing that a substantial proportion meet criteria for mild cognitive impairment compared with non-cancer controls. These impairments can profoundly impact daily functioning, occupational performance, social engagement, and overall quality of life, while also affecting adherence to follow-up care and participation in health-promoting behaviors [11,13]. Cross-sectional and longitudinal studies indicate that short-term memory, working memory, and verbal capacity are most frequently affected, followed by visual-spatial memory, executive functions, and attention. The severity of reported chemobrain symptoms is variable, ranging from subtle to more pronounced deficits. Due to the subtlety of some cognitive changes and the reliance on tests designed to detect more pronounced deficits, CRCI is often underrecognized or underestimated clinically. Prevalence estimates vary, with cognitive impairment detected in up to 30% of patients prior to chemotherapy and up to 75% during treatment, reflecting the high proportion of patients experiencing neurological complications in one or more cognitive domains. Subjective complaints are most frequently reported one month after chemotherapy, with some persisting chronically, although partially ameliorated over time [19,24].

3.4. Mechanisms of Chemotherapy-Related Cognitive Impairment

The pathophysiology of chemotherapy-related cognitive impairment (CRCI) is multifactorial, involving neurobiological, hormonal, and psychosocial mechanisms [11,12].

3.4.1 Biological contributors include neuroinflammation, oxidative stress, mitochondrial dysfunction, impaired neurogenesis, white matter microstructural alterations, vascular injury, and potential blood–brain barrier (BBB) dysregulation [19]. Chemotherapeutic agents—such as anthracyclines, alkylating agents, antimetabolites, and taxanes—exert neurotoxic effects through multiple processes, including BBB disruption, reactive oxygen species (ROS) generation, microtubule destabilization, impaired axonal transport, and reduced hippocampal neurogenesis, ultimately leading to white matter degeneration. Severity is influenced by cumulative dose, administration route, prior lesions, radiation, and drug interactions [12]. Some patients exhibit cognitive deficits prior to chemotherapy, suggesting contributions from cancer-related biological effects and psychological stress [15].

3.4.2 Hormonal factors, particularly chemotherapy-induced ovarian suppression or adjuvant endocrine therapy, may further influence synaptic plasticity and cognitive processing. Endocrine therapies (tamoxifen, aromatase inhibitors) reduce estrogen-dependent neuroprotection, impairing serotonergic and cholinergic signaling, dendritic spine formation, NMDA receptor function, and BDNF expression, resulting in deficits in memory, executive function, and mood regulation [19].

3.4.3 Psychosocial contributors include fatigue, sleep disturbances, anxiety, depressive symptoms, and chronic stress. These interact with biological and hormonal mechanisms to exacerbate cognitive vulnerability and account for heterogeneity in symptom severity and duration [11,13,19].

3.4.4 Neuroinflammatory pathways are activated by systemic chemotherapy via cytokines (IL-1β, IL-6, TNF-α, IFNγ), leading to glial activation, disrupted synaptic transmission, and altered monoaminergic signaling. Neuroimaging confirms glial activation in frontoparietal and limbic regions. Oxidative stress overwhelms antioxidant defenses, causing protein, DNA, and lipid damage, mitochondrial dysfunction, and apoptosis. The hippocampus and prefrontal cortex, due to high metabolic activity, are particularly vulnerable, resulting in deficits in synaptic plasticity, memory, and processing speed. Impaired oligodendrocyte function contributes to demyelination and white matter atrophy [20,30,31].

3.4.5 Emerging mechanisms include effects of targeted therapies (HER2-directed agents, CDK4/6 inhibitors) and immune checkpoint inhibitors, which can indirectly affect neural connectivity and elicit subclinical neuroinflammatory responses. Chemotherapy-induced gut dysbiosis may reduce beneficial commensals, compromising BBB integrity, microglial regulation, and neurotransmitter synthesis. Genetic and epigenetic variability (e.g., APOE, COMT, BDNF) further modulates individual susceptibility. Advanced neuroimaging (fMRI, DTI, PET, MRS) and ecological momentary assessment reveal white matter alterations, disrupted connectivity, and metabolic changes. AI-driven approaches integrating multimodal data hold promise for predicting cognitive decline, stratifying risk, and guiding personalized interventions. Digital therapeutics can optimize cognitive training based on performance, fatigue, and stress, enhancing neuroplasticity [28,36].

Overall, CRCI arises from converging neurotoxic, inflammatory, oxidative, hormonal, immune, and gut–brain mechanisms. Disruptions in synaptic function, myelination, neurogenesis, and network connectivity compromise hippocampal and prefrontal circuits. Genetic, epigenetic, and lifestyle factors modulate vulnerability. A comprehensive understanding of these pathways is essential for developing multifaceted interventions—including neuroprotective agents, cognitive rehabilitation, physical activity, dietary modulation, and stress reduction—aimed at preserving and restoring cognitive function in cancer survivors (29).

Table 1.

Mechanism	**Pathophysiological Processes**	**Affected Brain Regions/Systems**	**Clinical Correlates**
Direct neurotoxicity of chemotherapeutic agents	BBB disruption, microtubule destabilization, impaired axonal transport, reduced hippocampal neurogenesis	Hippocampus, prefrontal cortex, white matter tracts	Memory impairment, reduced processing speed

Neuroinflammation	Elevated cytokines (IL-1β, IL-6, TNF-α), microglial activation, altered monoaminergic signaling	Frontoparietal networks, limbic system	Fatigue, executive dysfunction, mood disturbances
Oxidative stress and mitochondrial dysfunction	ROS accumulation, DNA and lipid damage, apoptosis	High-metabolic regions (hippocampus, prefrontal cortex)	Impaired attention, reduced cognitive flexibility
White matter microstructural injury	Demyelination, oligodendrocyte dysfunction, decreased connectivity	Frontal, parietal, temporal white matter tracts	Slowed information processing, working memory deficits
Hormonal dysregulation	Reduced estrogen-mediated neuroprotection, altered serotonergic and cholinergic signaling	Hippocampus, cortical association areas	Memory decline, executive dysfunction
Gut–brain axis alterations	Chemotherapy-induced dysbiosis, impaired BBB integrity, altered neurotransmitter synthesis	Distributed cortical networks	Subtle cognitive changes, fatigue

Genetic and epigenetic susceptibility	Variability in APOE, COMT, BDNF, inflammatory gene pathways	Network-level vulnerability	Heterogeneous symptom severity
Psychosocial stressors	Chronic stress, sleep disruption, anxiety, depression	Functional connectivity alterations	Increased subjective cognitive complaints

Table 1. **Proposed Mechanisms Underlying Chemotherapy-Related Cognitive Impairment (CRCI)BBB –** blood–brain barrier; **BDNF –** brain-derived neurotrophic factor; **COMT –** catechol-O-methyltransferase**; CRCI –** chemotherapy-related cognitive impairment; **IL –** interleukin**; ROS –** reactive oxygen species**; TNF-α –** tumor necrosis factor alpha.

3.5 Prevalence and Epidemiology of CRCI

Despite extensive research on cognitive sequelae following breast cancer treatment, reported prevalence rates of cognitive deficits during and after therapy remain highly variable. While some patients demonstrate improvement over months or years post-chemotherapy, others experience persistent deficits that may last up to 21 years [11]. Many cross-sectional studies show that cognitive deficits after chemotherapy in women with breast cancer may range from 12% to even over 80%. Variability in prevalence is influenced by patient-specific factors, including age, baseline cognitive function, menopausal status, and educational attainment. Additionally, cognitive deficits may be present before chemotherapy initiation, potentially resulting from direct tumor effects, comorbidities, or psychological factors such as anxiety and fatigue [12,14].

3.6 Neuropsychological Symptoms and Quality of Life

The neuropsychological domains most commonly affected include visual processing, visuomotor coordination, executive functioning, and attentional control. Patients experience a spectrum of symptom severity, ranging from subtle cognitive disruptions to pronounced impairments. These deficits frequently manifest as generalized “mental fog,” word-finding

difficulties, transient confusion, and increased cognitive effort required for routine tasks [10,13]. Consequently, CRCI significantly impacts patients' quality of life (QOL) [14]. Insufficient information, limited awareness, and inadequate support from family members or healthcare providers may further exacerbate distress and restrict access to appropriate emotional and rehabilitative care [12].

3.7 Neuroimaging Findings and Brain Changes

Chemotherapeutic agents are associated with neurotoxicity, reflected in diffuse structural brain alterations, including white matter integrity disruptions and gray matter volume reductions. Task-based fMRI demonstrates functional abnormalities in regions involved in cognition [36]. Resting-state fMRI (rsfMRI) has revealed widespread alterations in intrinsic networks among breast cancer survivors, with some connectivity changes correlating with fatigue and sleep quality, particularly between frontal and parietal regions. Graph theory approaches model the brain as nodes (anatomical regions) and edges (connectivity), enabling visualization and quantitative characterization of network properties, including functional integration (global efficiency, path length) and segregation (clustering coefficient, local efficiency) [23]. Studies applying rsfMRI and graph theory in breast cancer patients report decreased global clustering, lower efficiency, and regional disruptions in frontal, temporal, striatal, occipital, and parietal hubs, correlating with cognitive impairments, especially memory deficits. However, the relative contributions of chemotherapy versus cancer pathogenesis remain incompletely defined, and most studies lacked baseline pre-chemotherapy characterization [18]. Structural and functional imaging consistently confirms brain changes linked to cognitive dysfunction. MRI analyses demonstrate reductions in gray matter volume and density, microstructural white matter alterations, and functional modifications across frontal, parietal, temporal, occipital, and cerebellar regions. These changes are particularly associated with deficits in executive function and memory in chemotherapy-treated patients compared with non-chemotherapy-treated patients or healthy controls [16,17].

3.8 Assessment and Interventions

Systematic assessment and monitoring of cognitive function are essential components of survivorship care. Objective neuropsychological testing, combined with patient-reported outcomes, can identify individuals at increased risk of persistent deficits [13]. Non-pharmacological interventions have demonstrated efficacy in improving both subjective and

objective cognitive outcomes. These include structured cognitive rehabilitation, supervised physical activity programs, mindfulness- based techniques, and psychosocial support [24]. Pharmacological treatments remain limited, and evidence supporting their routine use is insufficient. Longitudinal research integrating biomarkers, neuroimaging, and advanced cognitive assessment is necessary to delineate the natural history of CRCI, refine risk stratification, and guide the development of personalized preventive and therapeutic strategies [11,13].

3.9 Assessment of Chemotherapy-Related Cognitive Impairment Using Near-Infrared Spectroscopy (NIRS)

Research indicates that mild cognitive impairment following chemotherapy is more frequently reported by patients than detected by formal neuropsychological testing, and these subjective complaints often persist during and after treatment, substantially interfering with daily functioning and occupational performance [20]. Subjective cognitive functioning can be systematically evaluated using validated self-report instruments such as the Functional Assessment of Cancer Therapy Cognitive Function (FACTCog). The FACT-Cog allows multidimensional assessment of perceived cognitive impairment, capturing the patient's perspective on memory, attention, concentration, and mental clarity, and provides insight that may not always be reflected in standardized neuropsychological tests. The International Cancer and Cognition Task Force recommends using both subjective and objective cognitive assessment in patients undergoing chemotherapy [24,31]. In addition to self-reported measures, objective assessment often includes verbal fluency tasks, which are sensitive to executive dysfunction and frontal lobe involvement. Neuroimaging research has provided converging evidence that chemotherapy-related cognitive impairment is associated with functional alterations in the brain. Studies using structural and functional imaging techniques have demonstrated changes in cerebral activation patterns, particularly within frontal and temporal regions, during tasks requiring attention, multitasking, or verbal fluency. These alterations may underlie the diminished cognitive efficiency observed in patients receiving chemotherapy [31]. NIRS represents a non-invasive functional neuroimaging technique capable of detecting hemodynamic changes in cortical regions by measuring variations in oxygenated and deoxygenated hemoglobin. These parameters reflect regional cerebral blood flow and cortical activation. Evidence suggests that NIRS is sufficiently sensitive to detect subtle metabolic and hemodynamic changes during cognitive task performance, including verbal fluency paradigms. Near-infrared light (NIR) is able to penetrate biological tissues due to the relative transparency

of skin and bone within the so-called “optical window.” Although various chromophores in human tissue absorb NIR light, the technique most effectively measures absorption by oxygenated and deoxygenated hemoglobin (oxy-Hb and deoxy-Hb) using wavelengths in the 700–2500 nm range [32,33,34].

A total of 180 women with newly diagnosed breast cancer were enrolled in the study. Participants were divided into two groups: those undergoing chemotherapy and those not receiving chemotherapy. Subjective cognitive functioning was assessed using the FACT-Cog, particularly the Perceived Cognitive Impairment scale. Objective cognitive performance was measured using phonological and semantic verbal fluency tasks. Simultaneously, cortical activation in the dorsolateral prefrontal cortex was monitored using near-infrared spectroscopy. NIRS devices differ in technical characteristics; the system used in this study specifically measured regional oxygen saturation, a parameter sensitive to changes in oxygen delivery to cortical tissue. The findings demonstrated that a substantial proportion of participants met criteria for clinically significant perceived cognitive impairment. Women receiving chemotherapy reported greater cognitive difficulties, achieved lower scores on verbal fluency tasks, and exhibited reduced prefrontal cortical oxygenation compared to patients not treated with chemotherapy. A significant association was observed between lower subjective cognitive scores and both poorer task performance and decreased regional oxygen saturation, supporting concordance between patient reported outcomes and neurophysiological measures. Furthermore, cognitive impairment appeared to intensify with an increasing number of chemotherapy cycles. Patients exposed to four or more cycles demonstrated a more pronounced decline in both behavioral performance and cortical activation. Multi-agent chemotherapy regimens, including doxorubicin, cyclophosphamide, and docetaxel, were associated with greater cognitive vulnerability and reduced quality of life indicators. Overall, these findings support the concept that chemotherapy-related cognitive impairment is accompanied by measurable alterations in cortical hemodynamics, particularly within prefrontal regions subserving executive functions. The study also highlights the clinical relevance of integrating subjective cognitive assessment with objective neuropsychological testing and functional neuroimaging to obtain a comprehensive evaluation of cognitive outcomes in patients undergoing chemotherapy [19].

3.10 Assessment of Memory Deficits in Women with Breast Cancer Using Objective and Subjective Measures

Memory deficits in women with breast cancer have been investigated using both objective neuropsychological tests and subjective self-report instruments. Objective neuropsychological tests assess short-term, working, verbal, and visual memory using standardized batteries (WAIS, WMS, Rey AVLT). Subjective memory complaints are assessed with validated self-report scales, capturing perceived cognitive difficulties not always detected by objective tests. A total of 19 studies were included in a systematic review, comprising 9 longitudinal and 10 cross-sectional investigations published between 2007 and 2022. Sample sizes ranged from 38 to 1,477 participants, all women diagnosed with breast cancer, with mean ages between 49 and 62 years. Approximately 58% of the studies focused on patients undergoing chemotherapy. The review highlighted notable heterogeneity in study design, cognitive measures, and assessment timing, contributing to mixed findings across the literature. Despite this variability, most studies consistently reported impairments in short-term and working memory, particularly within the verbal domain, whereas visual memory outcomes appeared largely unaffected. Results indicated that both objective and subjective assessments detect memory deficits in women treated for breast cancer. Objective measures demonstrated decreases in short-term and working memory following chemotherapy, with some verbal working memory impairments persisting up to seven months post treatment. Subjective measures confirmed that patients reported more memory complaints following chemotherapy and surgery, with prospective memory complaints often more pronounced than retrospective. Furthermore, memory deficits were linked in some studies to wellbeing indicators, including depression, anxiety, and fatigue, particularly in chemotherapy-treated patients. These findings underscore the importance of assessing both objective and subjective cognitive outcomes to capture the full scope of cancer-related memory impairment [21,22].

Resting state functional magnetic resonance imaging (rs-fMRI) is a reliable and non-invasive method used to assess spontaneous neuronal activity during rest. In breast cancer patients assessed one month after conventional chemotherapy, overall cognitive function did not change significantly, but memory, attention, executive function, and processing speed were decreased. Resting state fMRI revealed abnormal activity in specific brain regions following chemotherapy. Areas with increased neural activity, indicated by elevated amplitude of low frequency fluctuations (ALFF), included the bilateral anterior cuneiform and the middle temporal gyrus [15,25,26].

3.11 Neuroimaging Based Biotypes for Precision Diagnosis and Prognosis of Breast Cancer Related Cognitive Impairment

Cancer related cognitive impairment is currently assessed using standardized neuropsychological tests and self report measures. Both approaches have important limitations. Objective tests may lack sensitivity and ecological validity. Subjective measures are influenced by affective and contextual factors. Objective and subjective assessments often do not correlate strongly. This suggests that they may reflect distinct neural phenotypes [35]. Traditional diagnostic approaches rely on dichotomous classifications such as impaired versus non-impaired. These classifications are frequently based on arbitrary cut offs. This binary framework does not capture the continuous and heterogeneous nature of cognitive function. As a result, meaningful subgroups of patients may remain unidentified. Data driven statistical techniques such as growth mixture modeling, latent profile analysis, and clustering have identified multiple cognitive subtypes of CRCI. Most investigations report three classes, although up to five subgroups have been described depending on methodology and sample characteristics. Neuroimaging research indicates that CRCI is a brain based condition characterized by structural and functional alterations. Structural MRI studies have shown reductions in gray matter volume and white matter integrity in patients treated with chemotherapy. Some of these changes persist long term. Diffusion tensor imaging studies demonstrate disrupted white matter microstructure. These findings suggest possible demyelination processes. Functional MRI studies show altered brain activation during cognitive tasks. In many cases, hyperactivation is observed despite preserved behavioral performance. This pattern is interpreted as compensatory neural effort. Resting state functional connectivity analyses reveal both hyperconnectivity and hypoconnectivity within large scale brain networks. These include frontoparietal networks and the default mode network. Such variability reflects biological heterogeneity and may explain differences in cognitive symptoms and test performance [27]. Neuroimaging findings across modalities are summarized in Table 2.

Table 2. Neuroimaging Modalities and Key Findings in Chemotherapy-Related Cognitive Impairment (CRCI)

Neuroimaging Modality	Primary Measure	Key Findings in CRCI	Affected Brain Regions / Networks	Clinical Interpretation
Structural MRI	Gray matter volume; white matter integrity	Reduced gray matter volume and structural alterations following chemotherapy; some changes persist long term	Frontal and temporal regions	Structural vulnerability underlying memory and executive dysfunction
Diffusion Tensor Imaging	White matter microstructure	Disrupted white matter microstructure suggestive of compromised connectivity	Frontotemporal pathways and large-scale cortical connections	Impaired network communication; possible structural disconnection
Task-based fMRI	Task-evoked cortical activation	Altered activation during cognitive tasks; hyperactivation despite preserved performance	Prefrontal cortical regions	Compensatory neural effort and reduced neural efficiency

Resting-State fMRI	Functional connectivity; intrinsic activity	Hyperconnectivity and hypoconnectivity within large-scale networks; abnormal intrinsic activity	DMN; frontoparietal networks	Network instability contributing to heterogeneous cognitive symptoms
Near-Infrared Spectroscopy	Cortical oxygenation (regional oxygen saturation)	Reduced prefrontal oxygenation during verbal fluency tasks; association with subjective cognitive complaints	Dorsolateral prefrontal cortex	Impaired cortical activation during executive processing
Imaging-Based Biotyping (Machine Learning / Clustering)	Connectivity-based subgroup identification	Identification of three distinct neuroimaging-based biotypes with different cognitive and clinical profiles	Network-level patterns derived from resting-state connectivity	Precision phenotyping and improved prediction of long-term cognitive outcomes

CRCI – chemotherapy-related cognitive impairment, **GM** – gray matter, **WM** – white matter, **MRI** – magnetic resonance imaging, **DTI** – diffusion tensor imaging, **fMRI** – functional magnetic resonance imaging, **Task-fMRI** – task-based functional MRI, **rs-fMRI** – resting-state functional MRI, **DMN** – default mode network, **PFC** – prefrontal cortex, **NIRS** – near-infrared spectroscopy, **ML** – machine learning

Biotping applies machine learning and clustering techniques to identify biologically defined subgroups based on shared patterns of brain structure and functional connectivity. In breast cancer survivors treated with chemotherapy, resting-state fMRI studies have identified three distinct neuroimaging-based biotypes, each characterized by specific cognitive, clinical, demographic, and psychological profiles. Unlike symptom-based classifications, which may group biologically heterogeneous individuals into a single impaired category, imaging-derived biotypes appear to capture mechanistic heterogeneity underlying CRCI.

Pretreatment neuroimaging markers further demonstrate potential for predicting long-term cognitive outcomes. Incorporating biotyping into predictive models may therefore enhance risk stratification and facilitate the development of personalized therapeutic strategies, as biologically distinct subgroups may differ in their responsiveness to cognitive rehabilitation, structured physical exercise, or neuromodulation interventions [27].

Cognitive performance in the reviewed studies was assessed using both standardized neuropsychological tests and self-report measures. Most investigations reported post-chemotherapy impairments in executive functioning, memory, attention, and processing speed. These cognitive domains correspond to frontoparietal and temporal brain systems, which are consistently implicated in resting-state analyses. Functional MRI studies reveal disrupted intrinsic connectivity and abnormal spontaneous activity, particularly within the default mode system. Seventy-five percent of reports described alterations involving regions associated with this system, with both reduced and increased connectivity patterns observed. This bidirectional pattern suggests a combination of functional disruption and compensatory cortical hyperactivation.

In sixty-three percent of studies, functional brain alterations were significantly associated with cognitive performance. However, several investigations did not detect clear correlations, indicating that functional dysregulation and measurable cognitive deficits are not invariably linearly related. The absence of consistent associations supports the hypothesis that clinically similar cognitive complaints may arise from heterogeneous neurobiological substrates [16].

Structural imaging findings complement these observations. Widespread functional disconnection across distributed cortical systems has been interpreted within a disconnection framework, whereby structural compromise impairs efficient communication across large-scale brain systems. Converging evidence indicates that structural vulnerability and resting-state

dysregulation particularly affect frontoparietal–temporal circuitry and the stability of the default mode system. These alterations are considered core neurobiological substrates of chemotherapy-associated cognitive change [27].

Despite consistent evidence of functional disturbance and reported cognitive decline, important limitations remain. Many studies are characterized by small sample sizes and methodological heterogeneity, and baseline as well as longitudinal assessments are frequently absent, limiting causal inference. Although current findings support a biological contribution of chemotherapy to cognitive impairment, definitive conclusions regarding causality cannot yet be drawn. Future research should integrate longitudinal resting-state neuroimaging, standardized neuropsychological evaluation, and data-driven biotyping approaches to enhance precision diagnostics and improve identification of patients at risk for persistent cognitive deficits [16,27].

Conclusion

Persistent cognitive dysfunction is a clinically significant late effect of systemic chemotherapy in a subset of breast cancer survivors. These deficits commonly affect memory, attention, processing speed, and executive function. They can persist for months or even years after treatment completion. The functional consequences are substantial, as cognitive impairments may reduce occupational performance, complicate management of daily tasks, limit social engagement, and impair health-related decision-making. This, in turn, diminishes overall quality of life and long-term functional independence. Both objective neuropsychological deficits and subjective cognitive complaints contribute to this burden. These findings underscore the importance of comprehensive cognitive assessment in survivorship care. Current evidence supports a multifactorial etiology. Chemotherapy-induced neurotoxicity, neuroinflammation, oxidative stress, mitochondrial dysfunction, structural and functional brain alterations, vascular injury, and hormonal changes interact with patient-specific vulnerability factors. Baseline cognitive reserve, age, comorbidities, genetic predispositions, and psychosocial stressors further modulate the severity and persistence of impairment. Hormonal therapies, particularly estrogen suppression, may exacerbate cognitive vulnerability by disrupting neuroprotective mechanisms. Emerging research also highlights the role of the gut-brain axis, which may influence cognitive outcomes through modulation of neuroinflammation and neurotransmitter availability. Systematic evaluation of cognitive function is essential for early identification and risk stratification. Integrating subjective assessments, such as patient-reported cognitive questionnaires, with objective neuropsychological testing and advanced

neuroimaging provides a multidimensional understanding of cognitive status. Resting-state functional MRI, diffusion tensor imaging, and machine learning-based biotyping have identified mechanistically distinct subgroups. These approaches enable precise prediction of cognitive trajectories and inform individualized interventions. Pharmacological treatments have shown limited and inconsistent efficacy, whereas non-pharmacological approaches demonstrate measurable benefits. Structured cognitive rehabilitation programs, supervised physical activity, mindfulness-based interventions, and psychosocial support improve both objective cognitive performance and patient-perceived cognitive function. These strategies may also mitigate fatigue, anxiety, and depression, which often exacerbate cognitive symptoms. Incorporating such interventions into survivorship care plans can preserve cognitive reserve, optimize daily functioning, and enhance long-term quality of life. Despite substantial progress, important gaps remain. The true prevalence of chemotherapy-related cognitive impairment is uncertain due to heterogeneity in study design, assessment tools, and diagnostic criteria. Large-scale longitudinal studies are needed to delineate temporal trajectories, identify reliable biomarkers, and clarify the relative contributions of chemotherapy versus cancer-related and psychosocial factors. Research targeting older survivors and individuals with pre-existing vulnerabilities is particularly warranted. Comparative studies of patients who have not received chemotherapy would improve understanding of cancer-related cognitive changes independent of systemic treatment. Future research should explore ecological cognitive monitoring, multimodal neuroimaging, and digital therapeutics. Tailored, evidence-based strategies for prevention and intervention can be developed by understanding individual susceptibility through genetic, epigenetic, and neuroimaging markers. Translating these insights into clinical practice has the potential to safeguard cognitive function, maintain functional independence, and optimize quality of life for long-term breast cancer survivors.

Disclosure

Author's contribution

Conceptualization: [WM], [EH], [NP]
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Software: [NP], [AD], [KK], [SK]
Check: [EH], [DP], [AD]
Formal analysis: [WM], [EH], [DP]
Investigation: [WM], [NP], [KK], [AD]

Resources: [SK], [NP], [KK]
Data curation: [EH], [WM], [DP], [AD]
Writing - rough preparation: [WM], [EH], [NP]
Writing - review and editing: [DP], [SK], [AD]
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