RESEARCH ARTICLE

Chemotherapy-Related Cognitive Impairment and Changes in Neural Network Dynamics

A Systematic Review

Sandra Leskinen,[1] Samir Alsalek,[2] Rosivel Galvez,[3] Favour C. Ononogbu-Uche,[1] Harshal A. Shah,[3] Morana Vojnic,[4] and Randy S. D'Amico[3]

Neurology® 2025;104:e210130. doi:10.1212/WNL.0000000000210130

Correspondence
Ms. Leskinen
sandra.leskinen@downstate.edu

Abstract

Background and Objectives

This systematic review aims to synthesize the current literature on the association between chemotherapy (CTX) and chemotherapy-related cognitive impairment (CRCI) with functional and structural brain alterations in patients with noncentral nervous system cancers.

Methods

A comprehensive search of the PubMed/MEDLINE, Web of Science, and Embase databases was conducted, and results were reported following preferred reporting items for systematic review and meta-analyses guidelines. Data on study design, comparison cohort characteristics, patient demographics, cancer type, CTX agents, neuroimaging methods, structural and functional connectivity (FC) changes, and cognitive/psychological assessments in adult patients were extracted and reported. Study quality was assessed using an adapted version of the Newcastle-Ottawa Scale (NOS) for observational studies. Qualitative synthesis of cognitive and psychological testing outcomes, functional and structural connectivity changes, and their associations with CRCI were performed.

Results

From 11,335 records identified, 63 studies analyzing 3,642 patients were included. Study designs included 24 prospective studies, 1 retrospective study, 36 cross-sectional studies, and 2 longitudinal studies. Most studies (75%) focused on patients with breast cancer. Common neuroimaging techniques included functional magnetic resonance imaging and diffusion tensor imaging. Postchemotherapy, many studies reported structural and FC alterations in brain networks such as the default mode, central executive, and dorsal attention networks. Cognitive function was assessed in 56 of the 63 included studies. Of the studies examining specific cognitive domains, 64% reported worsened learning and memory, 56% found impaired processing speed, and 70% identified deficits in attention/working memory in patients after CTX. Of the studies examining associations between connectivity changes and worsened cognitive function, 72% reported significant correlations in postchemotherapy patients. However, most of these studies were of low evidence, while 45% of high evidence–level studies, including prospective cohort studies, did not find significant associations between connectivity alterations and cognitive impairments.

Discussion

While there is evidence suggesting CTX affects brain connectivity and neural network dynamics that can lead to cognitive difficulties, the findings are inconsistent. More robust and standardized research is needed to conclusively determine the extent of these effects and to develop targeted interventions for mitigating potential cognitive impairments in patients undergoing systemic treatment.

RELATED ARTICLE

Editorial
Decoding Causes and Consequences in Chemotherapy for Non-CNS Cancer: Behind the Brain Fog
Page e210295

[1]State University of New York Downstate Medical Center, Brooklyn, NY; [2]Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA; [3]Department of Neurosurgery, Lenox Hill Hospital, Zucker School of Medicine at Hofstra/Northwell, New York, NY; and [4]Northwell Health Cancer Institute, Lenox Hill Hospital, Zucker School of Medicine at Hofstra/Northwell, New York, NY.

Glossary

ALFF = amplitude of low frequency fluctuation; **CEN** = central executive network; **CRCI** = chemotherapy-related cognitive impairment; **CTX** = chemotherapy; **DLPFC** = dorsolateral prefrontal cortex; **DMN** = default mode network; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FC** = functional connectivity; **GMD** = gray matter density; **MD** = mean diffusivity; **NOS** = Newcastle-Ottawa Scale; **NSD** = no significant difference; **RD** = radial diffusivity; **rs-fMRI** = resting state fMRI; **t-fMRI** = task-dependent fMRI; **WM** = white matter.

Introduction

Cancer is a leading cause of morbidity and mortality globally. In the United States alone, approximately 2 million people are diagnosed and half a million others will die from it every year, respectively.[1] Chemotherapy (CTX) is one of the more researched and effective therapies for cancer that is currently used, used independently or in conjunction with other modalities such as surgery or radiation.[2] Despite its efficacy as an anticancer therapeutic, CTX has been associated with a plethora of side effects such as nausea, vomiting, pain, fatigue, myelosuppression, and neuropathy.[2] One curious adverse effect of CTX is CTX-related cognitive impairment chemotherapy-related cognitive impairment (CRCI), colloquially referred to as "chemobrain." The mechanisms by which CRCI affects the CNS remain unclear.[3]

CRCI may present as a broad spectrum of cognitive dysfunction, ranging from memory lapses and attention deficits to impairments in executive function.[4] These disruptions to normal neurologic functioning can have profound implications on the quality of life of cancer survivors, with many patients experiencing lingering cognitive challenges long after transitioning into survivorship care. This concern is growing as cancer mortality rates decline, meaning that more individuals are at risk of experiencing the CRCI phenomenon.[1]

This review specifically focuses on CRCI in patients with non-CNS cancers, excluding cases of metastatic brain cancer. One method of evaluating CRCI in these patients is through neuromonitoring studies that examine changes in brain structure and function. This approach, aptly termed connectomics, provides valuable insights into the neural connections within the brain. Connectomics is the comprehensive study of the connectome, the intricate map of neural connections within the brain. It involves the use of advanced imaging techniques, such as functional MRI (fMRI) and diffusion tensor imaging (DTI), to visualize and analyze networks of neural pathways.[5] By understanding the connectome, researchers can gain insights into how CTX may disrupt neural connections that lead to cognitive impairments.[6] This systematic review attempts to collate and analyze the current body of literature pertaining to CRCI in non-CNS cancers, focusing on alterations in the brain's connectivity secondary to CTX and their effects on patients' cognition and quality of life.

Methods

Study Collection

An extensive review of published studies was conducted, and the findings were reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. This review was not prospectively registered. MEDLINE/PubMed (1974–2023), Web of Science (1998–2023), and Embase (1996–2023) were queried using the terms: ("chemotherapy" OR "systemic therapy" OR "chemobrain" OR "chemo fog" OR "chemotherapy-related cognitive impairment" OR "chemotherapy-induced cognitive impairment") AND ("cognitive" OR "neurological") AND ("impairment" OR "dysfunction" OR "deficit" OR "change" OR "abnormality") AND ("anatomical mapping" OR "brain networks" OR "connectivity" OR "connectome" OR "connectomics" OR "diffusion imaging" OR "functional MRI"). Default search timeframes are provided in parentheses beside each database. The final search was conducted on October 9, 2023.

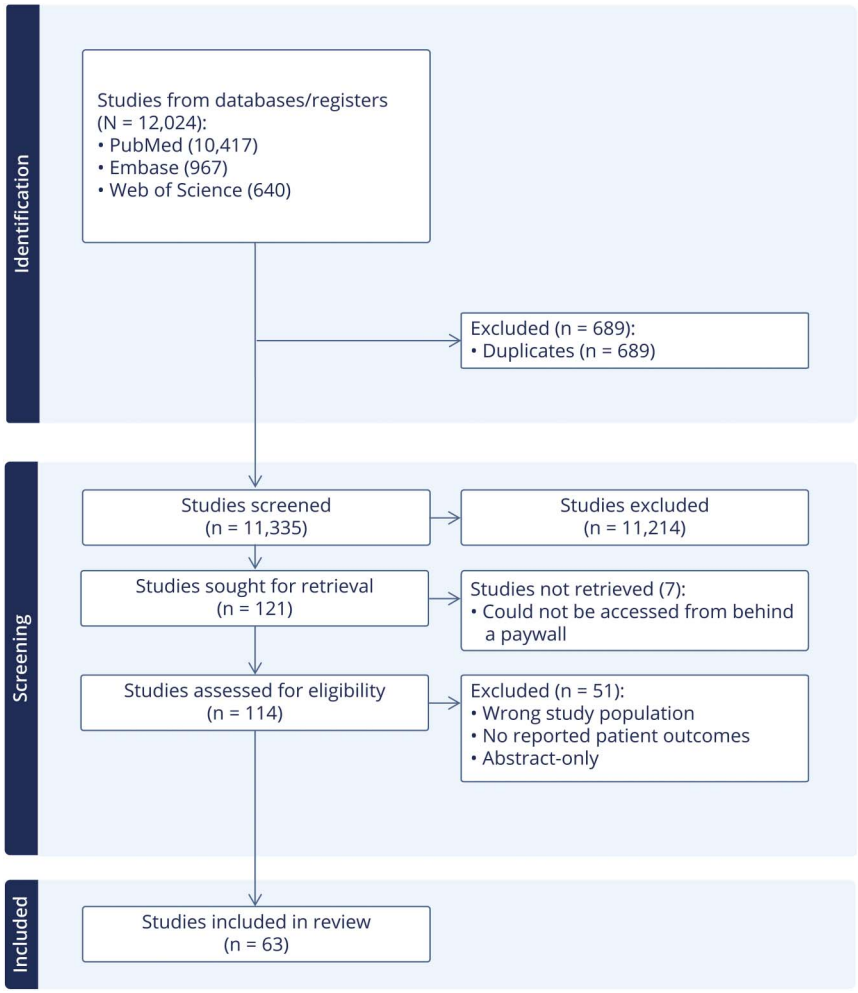
Study Selection

The titles and abstracts of the resulting articles were screened for inclusion by 4 independent reviewers (S.L., S.A., F.C.O.-U., and R.G.). English in vivo prospective studies, retrospective studies, randomized controlled trials, and case series/case studies relating to impairment secondary to CTX and to connectomics and its associated terms in the title and/or abstract were further scrutinized for eligibility. Non-English studies, ex vivo studies, in vitro studies, pediatric studies, animal studies, feasibility studies, pilot studies, editorials, commentaries, and abstract-only or conference-only publications were excluded. The abstracts of screened studies were further analyzed and included in the final analysis if they examined structural and/or functional connectivity (FC) and reported outcomes in adult patients. Any conflicts were resolved by a senior author (R.D.). The search is fully reported in Figure.

Data Extraction

Included studies were categorically analyzed by each reviewer, and study characteristics were abstracted, including study design, chemotherapeutic agents used, type of primary cancer, pretreatment disease stage, neuroimaging methods, total cohort size, mean age, previous treatment status, number of patients undergoing CTX treatment, patients undergoing non-CTX treatment, and healthy controls. Level of evidence

Figure PRISMA Flow Diagram of the Search Algorithm and Exclusion Criteria Used in This Review



PRISMA = preferred reporting items for systematic review and meta-analyses.

was also characterized for each study according to the Oxford Centre for Evidence-Based Medicine (OCEBM): Levels of Evidence criteria.

Fifty-six studies included cognitive and/or psychological data. Recognizing that there is no single consensus on the organization of cognitive and psychological assessment into functional domains, we relied on an established framework from the literature.[7] Each test was assigned to a specific domain based on this framework, and the initial assignments were independently reviewed by all team members. Discrepancies were discussed and resolved through consensus. If reasonable consensus could not be reached, 2 senior authors were asked to evaluate and resolve the conflict (M.V. and R.D.). This methodical approach allowed us to compile the assessments into 8 cognitive/psychological domains, which are presented in Table 1.

Quality Assessment

For nonrandomized observational studies, including cohort and cross-sectional designs, we adapted the Newcastle-Ottawa Scale (NOS) to account for additional quality indicators relevant to our review. Among other variables, we considered the selection and comparability of study groups, the validity of the methods used to ascertain exposures or outcomes, the adequacy of follow-up, and the appropriateness of statistical analyses. Each study was scored to a maximum possible score of 26 points. This quality assessment was applied consistently across all included studies, and the questionnaire can be found in supplementary material, eAppendix 1.

Standard Protocol Approvals, Registrations, and Patient Consents

Not applicable to this review.

Data Availability

Data extracted from studies can be found in eTables 1–4, and quality assessments for each study can be found in eTable 5. The NOS quality assessment questionnaire can be found in eAppendix 1.

Table 1 Categorization of Each Cognitive and Psychological Assessment Into a Functional Domain

Cognitive or psychological domain	Assessments
Learning and memory	WMS-III Visual Reproduction, Wechsler Memory Scale-Revised Visual Reproduction Test (WMS-R Visual Reproduction Test), Memory Functioning Questionnaire (MFQ), Multifactorial Memory Questionnaire Ability Scale (MMQ), Prospective and Retrospective Memory Questionnaire (PRMQ), California Verbal Learning Test (CVLT), Wechsler Memory Scale-III (WMS-III), Hopkins Verbal Learning Test (HVLT) and the revised edition (HVLT-R), Brown Learning Test (BLT), and Rey-Kim Auditory Verbal Learning Test (RAVLT)
Language	Controlled Oral Word Association Test (COWAT), Boston Naming Test (BNT), Verbal Fluency Test (VFT), and Delis-Kaplan Executive Function System Verbal Fluency Test (D-KEFS VF)
Processing speed	Coding subset of the Wechsler Adult Intelligence Scale Third or Fourth Editions (WAIS-III/IV), Digital Symbol Substitution Test (DSST), and Trail Making Test Part A (TMT-A)
Executive function	Trail Making Test Part B (TMT-B), Modified Card Sorting Test (MCST), Wisconsin Card Sorting Test (WCST), Behavioral Regulation Index (BRI), Behavioral Rating Inventory of Executive Function (BRIEF), Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test, D-KEFS Sorting Test, D-KEFS Trail Making Test, General Executive Composite (GEC), and Clock Drawing Test (CDT)
Attention/working memory	Digit Span and Letter Number Sequence subsets of the WAIS-III/IV, Attentional Function Index (AFI), Digit Span Test (DST), Brief Test of Attention (BTA), Number Connection Test A (NCT-A), Test of Everyday Attention (TEA), Bourdon-Wiersma Dot Cancellation Test (BWDCT), Paced Auditory Serial Addition Test (PASAT), Verbal Working Memory Task (VWMT), and Stroop Color and Word Test (SCWT)
Overall and subjective cognitive function	Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Global Rating of Cognition (GRC), Mattis Dementia Rating Scale-2 (MDRS-2), MicroCog: Assessment of Cognitive Functioning (MicroCog), Medical Outcomes Study-Cognitive Functioning Scale-revised (MOS-Cog), Cognitive Functioning Scale (CFS), and Global Deterioration Scale (GDS), Multiple Ability Self-Report Questionnaire (MASQ), and Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)
Mood (anxiety and depressive symptoms)	Three Item Worry Index (TIWI), Beck Anxiety Inventory (BAI), Hamilton Anxiety Rating Scale (HAMA), Self-Rating Anxiety Scale (SAS), State-Trait Anxiety Inventory (STAI), Weinberger Adjustment Inventory (WAI), Hospital Anxiety and Depression Scale (HADS), Hopkins Symptom Checklist-25 (HSCL-25), Beck Depression Inventory (BDI), Clinical Assessment of Depression (CAD), Center for Epidemiologic Studies-Depression Scale (CES-D), Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS), Patient Health Questionnaire (PHQ-8/9), Self-Rating Depression Scale (SDS), Profile of Mood States (POMS), and Impact of Event Scale-revised (IES-R)
Quality of life	Functional Assessment of Chronic Illness Therapy (FACIT), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Fatigue Assessment Scale (FAS), Piper Fatigue Scale-Revised (PFS-R), Fatigue Symptom Inventory (FSI), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30), Questionnaire of Self-Representations (QSR), Pittsburgh Sleep Quality Index (PSQI), and Perceived Stress Score (PSS)

Results

Search Results

A total of 11,335 unique articles were identified in the initial search. After screening titles and abstracts, 63 studies were included in this review, analyzing a total of 3,642 unique patients. Among the included studies were 24 prospective studies, 1 retrospective study, 36 cross-sectional studies, and 2 longitudinal studies. Studies examining the effects of CTX on patients with breast cancer predominated (n = 47). Nine studies reported on lung cancer, both non-small cell and small cell. Two studies examined gynecologic cancers. The rest examined testicular, colorectal, gastric cancers, and lymphoma, and 1 did not specify cancer type.

Of the 63 studies, 37 compared patients with cancer treated with CTX with healthy controls. Eighteen studies compared patients with cancer treated with CTX with cancer patients treated without CTX and healthy controls. Six studies compared patients with cancer treated with and without CTX. One study compared patients with cancer treated with CTX who self-reported cognitive impairment with those who did not self-report cognitive impairment. One study examined a series of CTX-treated patients with cancer.

Neuroimaging changes attributable to CTX were assessed in all included studies, using MRI techniques such as structural and fMRI and diffusion MRI techniques such as DTI.

Of the 24 studies including non-CTX patients with cancer as a control group, 15 studies were cross-sectional, 1 longitudinal, and 8 prospective. Five assessed activation changes through task-dependent fMRI (t-fMRI), 6 assessed white matter (WM) integrity through DTI and MRI, and 13 assessed network changes primarily through resting state fMRI (rs-fMRI). Thirteen of 24 studies reported connectivity findings in both CTX and non-CTX groups and 21 of 24 studies compared differences in cognitive findings in CTX vs non-CTX groups.

The following sections will attempt to detail, summarize, and synthesize study results according to cognitive/psychological domain changes, structural and FC alterations, and their significant associations or correlations following CTX treatment. Additional data on included studies can be found in supplementary material, eTables 1 and 2.

Quality Assessment Results

Twenty-five studies were classified as high quality, achieving scores ranging from 22 to 23 points out of 26. These high-

quality studies largely comprised prospective cohort studies and 1 longitudinal study, which were characterized by rigorous methodological approaches, effective management of confounding variables, and robust statistical analyses.

By contrast, 38 studies were rated as moderate quality, with scores between 18 and 21 points. This group included most of the cross-sectional studies, which were more susceptible to biases inherent in their design. Scoring for each study can be found in supplementary material, eTable 5.

Cognitive and Psychological Domain Changes Postchemotherapy

Fifty-six of 63 studies included cognitive and/or psychological data, which we distributed into 8 domains: (1) learning and memory, (2) language, (3) processing speed, (4) executive function, (5) attention/working memory, (6) overall and subjective cognitive function, (7) mood (including anxiety and depressive symptoms), and (8) quality of life (Table 2; additional data in supplementary material, eTable 3). Thirty-one of these studies were cross-sectional, 2 were longitudinal, 1 retrospective, and 22 prospective. These studies ranged from moderate to high quality. Thirty-one studies compared CTX patients with healthy controls, 6 compared patients with cancer treated with and without CTX, 17 compared CTX patients, non-CTX patients, and healthy controls, 1 compared self-reported cognitive impairment in CTX patients, and 1 reported on CTX patients only.

Among the 8 domains analyzed, only learning and memory, processing speed, and attention/working memory consistently showed worsened performance in CTX groups. Notably, most of the studies found No Significant Difference (NSD) between CTX and control groups in several domains, including language, executive function, mood, and quality of life (Table 2). The studies convey great variability in the effects of CTX across cognitive and psychological domains.

Learning and Memory

Twenty-five studies evaluated learning and memory. Of these, 16 studies (64%) reported significantly worse performance in CTX groups compared with control groups, and 9 studies reported NSD between groups.

Language

Six studies examined language. Two studies (33.3%) reported significantly worse performance in the CTX groups, while 4 studies reported no difference.

Processing Speed

Eighteen studies evaluated processing speed. Ten studies (56%) reported significantly worse processing speed in CTX groups, while 8 studies reported NSD between groups.

Executive Function

Twenty-seven studies evaluated executive function. Twelve studies (44%) reported worse executive function in the CTX groups, while the remaining 15 studies reported no difference.

Attention/Working Memory

Twenty studies evaluated attention. Fourteen studies (70%) reported significantly poorer attention in the CTX groups, and 6 studies reported NSD between groups.

Overall and Subjective Cognitive Function

Thirty-five studies evaluated overall and/or subjective cognitive function. Of these, 10 studies reported significantly worse overall cognitive function and 7 studies reported

Table 2 Cognitive and Psychological Domains Affected by Chemotherapy (CTX)

Cognitive/psychological domain	Total reporting studies	Worse performance in CTX group vs all controls	Worse performance in CTX group vs non-CTX group only	Worse performance in CTX group vs healthy controls only	Worse performance in both CTX and non-CTX groups vs healthy controls	No significant difference
Learning and memory	25	0	3 (12)	13 (52)	0	9 (36)
Language	6	0	0	0	2 (33.3)	4 (66.7)
Processing speed	18	1 (5.6)	2 (11.1)	7 (38.9)	0	8 (44.4)
Executive function	27	3 (11.1)	2 (7.4)	9 (33.3)	0	13 (48.1)
Attention/working memory	20	0	2 (10)	12 (60)	0	6 (30)
Overall and subjective cognitive function	35	2 (5.7)	3 (8.6)	10 (28.6)	3 (8.6)	17 (48.6)
Mood	31	1 (3.2)	0	5 (16.1)	2 (6.5)	23 (74.2)
Quality of life	19	2 (10.5)	0	5 (26.3)	2 (10.5)	10 (52.6)

This table summarized the number of studies reporting either significant declines or no significant differences in cognitive and psychological domains after chemotherapy. The performance of the chemotherapy group is compared with all controls, nonchemotherapy cancer patient controls, and healthy controls. The data are reported as the number of studies (n) and percentage (%). Domains assessed include learning and memory, language, processing speed, executive function, attention/working memory, overall and subjective cognitive function, mood, and quality of life.

significantly worse subjective cognitive performance in the CTX groups, compared with control groups. One study reported both worsened overall and subjective cognitive function. Conversely, 17 studies found NSD.

Mood

Thirty-one studies evaluated anxiety or depression. Of these, 5 studies reported significantly more anxiety and depressive symptoms, and 3 studies reported significantly more depressive symptoms alone in CTX groups, compared with controls. Conversely, 23 studies (74%) reported NSD between groups regarding these measures.

Quality of Life

Nineteen studies evaluated quality of life, fatigue, and stress. Seven of these studies (37%) found significantly higher fatigue and lower quality of life in the CTX groups, 2 found higher levels of stress, and 10 studies reported no significant difference.

Functional and Structural Connectivity Changes Postchemotherapy

We examined the effects of CTX on brain connectivity as captured by neuroimaging techniques such as rs-fMRI, t-fMRI, structural MRI, and DTI. Studies reported changes in structural connectivity, including WM integrity and gray matter density (GMD), and FC, including resting-state network and activation area changes. Additional data can be found in supplementary material, eTable 4.

White and Gray Matter Changes

Eleven studies examined white and gray matter changes through DTI and structural MRI. Seven were cross-sectional in design, 3 prospective, and 1 longitudinal. All ranged from moderate to high quality. Five studies compared CTX patients with healthy controls, 5 compared CTX patients, non-CTX patients, and healthy controls, and 1 compared CTX and non-CTX patients only.

Several studies indicated a decrease in fractional anisotropy (FA), a DTI measure of WM integrity, in numerous brain regions. Two cross-sectional and 2 prospective studies reported lower FA in the left inferior longitudinal fasciculus,[8] genu of the corpus callosum,[9] right superior longitudinal fasciculus,[10] and bilateral posterior cingulate gyri and dorsal thalamus.[11] Two other studies reported diffuse decreased FA in frontal, temporal, frontoparietal, and occipital WM tracts.[12,13] One cross-sectional study observed an 8.6% mean decrease in FA in areas like the left anterior corona radiata, left external capsule, and bilateral posterior thalamic radiation in CTX patients vs non-CTX patients.[14]

In addition to decreased FA, increased mean diffusivity (MD) and radial diffusivity (RD) were commonly reported, indicating disrupted WM microstructure. One cross-sectional study observed increased MD in frontal WM,[12] while a prospective study saw widespread higher MD.[10] More specifically, another prospective study reported increased MD and RD values in the genu of the corpus callosum,[15] and a cross-sectional study saw increased MD and RD in the retrolenticular portion of the bilateral internal capsules and posterior thalamic radiations.[14]

Some studies highlighted changes in GMD alongside WM alterations, with reductions reported in GMD in the left lateral posterior parietal cortex, bilateral cerebellum,[14] bilateral insulae, bilateral parahippocampal gyri, and left anterior cingulate cortex.[8]

Activation Changes

Fourteen studies—9 cross-sectional and 5 prospective of moderate-high quality—evaluated regional activation changes by using t-fMRI and structural MRI. Eight studies compared CTX patients with healthy controls, 4 studies compared CTX patients, non-CTX patients, and healthy controls, and 2 compared CTX and non-CTX patients only.

Changes in regional brain activation were increased, decreased, or mixed. Of these, 4 reported increases in activation within the postchemotherapy groups, including heightened activity in the temporal, frontal, parietal, and cerebellar regions[16] with specific increases in activation in the bilateral inferior parietal cortex, precuneus, and superior parietal cortex,[17] and right middle frontal and precentral gyri.[18] One prospective study identified varied activation in the frontoparietal region at 1-year postchemotherapy.[19] Conversely, 5 studies reported overall hypoactivation in regions of the frontal, temporal, parietal lobes, and cerebellum, with specific changes in the bilateral insulae, left inferior orbitofrontal cortex, bilateral middle temporal gyri,[20] and right dorsolateral prefrontal cortex (DLPFC).[21,22]

Two studies presented mixed activation patterns. One, a prospective study, found decreased activation in the left inferior frontal and posterior middle gyri 1 month postchemotherapy, but increased activation in the right cerebellar and left inferior precentral gyrus.[23] At 1 year, they observed increased activity in various frontal regions.[23] The other, a cross-sectional study, saw decreased activation in frontal, parietal, and temporal cortices, and the striatum, but increased activation in the left parietal operculum.[24]

Network Disruptions

Thirty-nine studies assessed changes in network connectivity primarily through rs-fMRI and structural MRI. Twenty-one of these studies were cross-sectional, 16 prospective, 1 retrospective, and 1 longitudinal, all ranging from moderate to high quality. Twenty-four studies compared CTX patients with healthy controls, 9 compared CTX patients, non-CTX patients, and healthy controls, 4 compared CTX and non-CTX patients only, 1 evaluated only CTX patients, and 1 compared CTX patients with and without self-reported cognitive impairment. The most scrutinized network was the default mode network ([DMN]; n = 12), followed by the central executive network ([CEN]; n = 4), and dorsal attention network (n = 4).

Twelve studies described varying patterns of alterations in the DMN. One cross-sectional study identified lower DMN connectivity in various regions in the frontal and parietal lobes.[25] Another cross-sectional study described both decreased and increased amplitude of low frequency fluctuation (ALFF) and regional homogeneity (ReHo) values in different regions of the bilateral frontal lobes,[26] and a prospective study observed ALFF increases in temporal regions and bilateral precuneus.[27] Notably, longitudinal studies disagreed on regained connectivity over time, with 1 reporting decreased DMN patterns from 1 month to 1 year postchemotherapy without return to baseline,[28] while another found decreased FC in the anterior and posterior DMN 1-week after CTX with increases in FC at 6 months.[29]

Connectivity Changes Reported in Patients With Cancer Treated With and Without CTX

Thirteen studies assessed structural and FC changes in patients with cancer treated with and without CTX. While the direction of these changes—whether increased or decreased—varied across studies, both groups exhibited alterations in key connectivity metrics.

As outlined in Table 3, the differences in the number of studies reporting changes between CTX and non-CTX groups were relatively small. For example, 3 studies reported changes in WM integrity in CTX patients, compared with 2 studies in non-CTX patients. Alterations in GMD, metabolism, and ALFF were observed in both groups, with 1 study

Table 3 Connectivity Metric Changes in Patients With Cancer Treated With and Without Chemotherapy

Connectivity metric	Studies reporting changes in CTX patients with cancer (n)	Studies reporting changes in non-CTX patients with cancer (n)	Detailed results in CTX patients	Detailed results in Non-CTX patients
White matter integrity	3	2	Decreased FA in corona radiata, corpus callosum, and superior longitudinal fasciculus (Deprez 2012); Decreased FA in right superior longitudinal fasciculus and increased MD in right corticospinal tract (Menning 2018); Lower FA and higher AD in left inferior longitudinal fasciculus (Simo 2015)	No significant changes in FA (Deprez 2012); Lower FA and higher AD in various regions (Simo 2015); Decreased FA and increased MD in genus of corpus callosum (Menning 2018)
Gray matter density	1	1	Decreased GMD in bilateral insulae, parahippocampal gyrus, and anterior cingulate cortex (Simo 2015)	Decreased GMD in left insula, parahippocampal gyrus, and anterior cingulate cortex (Simo 2015)
Functional connectivity	4	3	Decreased FC between posterior cingulate cortex and anterior cingulate cortex; increased FC with postcentral gyrus (Zhang 2020); Decreased FC in frontoparietal regions (Kardan 2019)	Decreased FC between posterior cingulate cortex and middle temporal gyrus; increased FC with postcentral gyrus (Zhang 2020); No significant changes (Kardan 2019)
Metabolism	1	1	Hypometabolic network in prefrontal cortex and cerebellar areas (D'Agata 2013)	Equally hypometabolic in parietal areas and frontal eye field (D'Agata 2013)
ALFF	1	1	Increased mfALFF in frontoparietal and occipital lobes (Shen 2021)	Increased mfALFF in frontoparietal lobe (Shen 2021)
ReHo	1	0	Increased mReHo in frontoparietal lobe (Shen 2021)	No change in ReHo (Shen 2021)
Activation	3	2	Increased activation in bilateral inferior parietal cortex and precuneus with task load (Menning 2017); Decreased left inferior frontal activation, increased thalamic activation (McDonald 2012)	Decreased right inferior parietal cortex activation with task load (Menning 2017); Increased left frontal activation (McDonald 2012)
Cerebral blood flow	1	0	Higher cerebral blood flow in insula, caudate, occipital gyrus, and temporal gyrus (Zhang 2022)	No changes in cerebral blood flow connectivity (Zhang 2022)

Using the 13 studies that included patients with cancer not treated with chemotherapy as a control group, this table compares the number of studies reporting changes in various connectivity metrics between patients with cancer who received chemotherapy (CTX) and those who did not (non-CTX). Metrics include White Matter Integrity, Gray Matter Density, Functional Connectivity, Amplitude of Low-Frequency Fluctuation (ALFF), Regional Homogeneity (ReHo), Activation, and Cerebral Blood Flow. Detailed findings are provided for each group.

reporting changes in each group for these metrics. Functional connectivity changes were slightly more frequent in CTX patients (4 studies) compared with non-CTX patients (3 studies). However, some connectivity metrics such as ReHo and cerebral blood flow changes were only reported in CTX patients, although these were based on a very limited number of studies. Activation changes were documented in both groups, with 3 studies in CTX patients and 2 in non-CTX patients. The reported changes for each group are included in eTable 4.

Trends in Association Between Connectivity and Cognitive/Psychological Test Performance Postchemotherapy

Forty-three studies examined associations between connectivity and cognitive or psychological assessment performance in patients treated with CTX. All were of moderate to high quality. Of the 31 studies that observed associations or significant differences between CTX-treated patients and patients with cancer who did not undergo CTX treatment and/or healthy controls, 18 studies examined changes in RSNs through rs-fMRI, 5 studies looked at WM changes, and 8 studies examined miscellaneous changes in activation areas via t-fMRI and GMD changes through structural MRI (Table 4; additional data can be found in supplementary material, eTable 4). Among all studies that evaluated both connectivity and cognitive/psychological performance, 12 studies (28%) did not find any associations between connectivity alterations and cognitive impairments (Table 4). Among only high evidence level studies (i.e., prospective studies), 9 of 20 total studies (45%) did not observe any associations (Table 5).

Changes in WM Integrity and GMD

A cross-sectional study assessing the relationship between WM integrity and scores on the Digit Span Test concluded that poor processing speed in patients postchemotherapy was associated with decreased WM integrity.[30] Similarly, correlations of FA changes with altered attention and processing speed were found in temporal and parietal WM tracts in 1 study[12] and correlations of mean regional FA changes with verbal memory in another.[13] Changes in attention were sometimes accompanied by an increase in self-reported cognitive complaints, including increased distractibility and trouble with word finding, at different timepoints after CTX treatment.[13] In assessments of memory, a prospective study observed that lower FA values in bilateral posterior cingulate gyri were positively correlated with changes in Auditory-Verbal Learning Test scores.[11] However, some studies reported WM changes but observed no significant correlations between cognitive test scores and DTI values in the CTX group.[10,15]

Decreased GMD and hypoactivation were observed in regions related to working memory and verbal fluency after CTX, suggesting an association between GMD changes and declines in cognitive performance in some studies.[8,21,31,32]

Regional Activation Alterations

In studies assessing activation areas through tests of executive function through t-fMRI, a high-quality prospective study reported increased parietal activation with increasing executive function task load, coupled with higher levels of fatigue and subjective complaints of cognitive decline in CTX patients.[17] Two studies saw DLPFC hypoactivation that correlated significantly with subjective[33] and objective decreases in executive function.[14]

Disruptions to Resting-State Networks

Studies assessing RSNs commonly found post-CTX alterations in FC in regions of the prefrontal cortex.[34–40] In

Table 4 Relationship Between Connectivity Alterations and Cognitive Changes in Chemotherapy-Treated Patients With Cancer

Structural or functional connectivity metric	Studies reporting changes in connectivity (n)	Studies reporting corresponding cognitive/psychological changes (n)	Studies reporting no significant differences or correlations (n)
White matter integrity	7	5	2
Gray matter density	3	2	1
Default mode network	6	3	3
Dorsal attention network	2	2	0
Central executive network	2	2	0
Salience network	1	1	0
Hippocampal network	1	1	0
Other networks	15	9	6
Activation	4	4	0

Abbreviation: CTX = chemotherapy.
Of 63 studies, 43 reported structural (gray matter density, white matter integrity) or functional (activation, networks) connectivity alterations and corresponding cognitive or psychological changes in CTX patients. Specific resting-state networks (e.g., default mode network, dorsal attention network, central executive network) are indicated when reported.

Table 5 Relationship Between Connectivity Alterations and Cognitive Changes in Chemotherapy-Treated Patients With Cancer in High Evidence Studies

Study	Study quality	WM, GMD, RSNs	CTX group connectivity changes	Association of connectivity with test performance in CTX group
Chen, Ye 2020	High	WM integrity	At 1 mo, mean MD and RD values in the genu of the corpus callosum increased (vs HC)	NSD or correlations
Menning 2018	High	WM integrity	Decreased FA in right superior longitudinal fasciculus and increased MD in right corticospinal tract (vs non-CTX) at 1 y. Widespread higher MD (vs HC)	NSD or correlations
Tong 2020	High	WM integrity	Lower N-acetylaspartate values in bilateral posterior cingulate gyrus and dorsal thalamus. Lower FA values in bilateral posterior cingulate gyrus	Positive correlations between changes in AVLT recognition and changes in NAA and FA values in bilateral posterior cingulate gyrus
Bai 2021	Moderate	Other networks	Increased ReHo in bilateral orbital frontal, DLPFC regions, decreased in middle frontal gyrus, right superior temporal gyrus, and right middle temporal gyrus	NSD or correlations
Chen 2019	High	Other networks	Increased ALFF in bilateral subcallosal gyri and decreased fALFF in left precuneus. No ReHo changes	NSD or correlations
Chen, Chen, Deng 2022	High	Other networks	Longitudinal signal decreases in right middle occipital and temporal gyri	Significant negative correlations between the cognitive function scores and SDBOLD values at the right inferior occipital and the right middle temporal gyri
Feng 2020	High	Other networks	NSD in FC vs HC at baseline. Post-CTX: increased FC in the left hippocampus and left insula; left anterior hippocampal and left middle temporal gyrus/temporal pole of superior temporal gyrus; right hippocampus and left Heschl gyri/insula; right posterior hippocampal and left superior temporal gyrus/left Heschl gyri	NSD or correlations
Feng, Wang 2020	High	Other networks	Altered FC in the left and right frontoparietal network, visual network, and self-referential network. Post hoc test showed decreased FC in LFPN, RFPN, SRN, and CEN 1 wk after chemotherapy and increased 6 mo after chemotherapy	Negative correlation of decreased CEN FC changes with increased DST score changes. Negative correlation of decreased FC changes of SMN/visual network with decreased SDS scores. Negative correlation of increased FC changes of the right calcarine sulcus cortex with decreased changes of SCWT.
Hu 2022	High	Other networks	Decreased degree centrality values of the right middle frontal gyrus and left precentral/middle frontal gyrus. Decreased GMD of right middle frontal gyrus and left precentral/middle frontal gyrus. Decreased FC between left precentral/middle frontal gyrus and bilateral precuneus	NSD or correlations
Kardan 2019	High	Other networks	FC decreases in frontoparietal regions at 1 mo, with increases at 7 mo	Improvement of cognitive health over time was paralleled by a disruption and later recovery of resting-state FC in the parietal and frontal brain regions
Kim 2016	High	Other networks	Decreased ReHo (vs HC) in bilateral frontal areas, increased ReHo in cuneus. Decreased ALFF in bilateral frontotemporal areas, increased ALFF in the posterior temporo-parieto-occipital areas. Decreased fALFF at the anterior cingulate and bilateral orbitofrontal gyrus, increased at right cerebellum, perirolandic, and temporo-occipital areas	Significant association of lower ALFF in the left inferior frontal gyrus with poor performance of the SCWT.

Continued

Table 5 Relationship Between Connectivity Alterations and Cognitive Changes in Chemotherapy-Treated Patients With Cancer in High Evidence Studies *(continued)*

Study	Study quality	WM, GMD, RSNs	CTX group connectivity changes	Association of connectivity with test performance in CTX group
Mo 2017	High	Other networks	Increased ReHo in the anterior and posterior lobes of the cerebellum, decreased in the right orbitofrontal area, right middle and superior temporal gyrus, right subcentral area (between the insula and postcentral/precentral gyrus), and left DLPFC and precentral gyrus	NSD or correlations
Perrier 2022	High	Other networks	Lower connectivity (vs HC) between the dorsal anterior cingulate cortex and multiple regions including the superior parietal lobule extended to the precuneus and between the dorsomedial prefrontal cortex and the precuneus and lingual gyrus extended to the posterior cingulate cortex	Negative correlation of anterior cingulate FC with QSR scores
Chen 2022	High	DMN	At 1 mo: increased FC in subnetworks of bilateral frontal lobes and right temporal lobe, decreased connectivity in subnetworks of medial prefrontal cortex, left temporal lobe, and retrosplenium. Increased FC to the anterior region and decreased FC to the posterior region of anterior cingulate cortex. DMN FC diminished from baseline to 1 mo	NSD or correlations
Feng, Wang 2020	High	DMN	Altered FC in the ADMN/PDMN. Post hoc test showed decreased FC in ADMN/PDMN 1 wk after chemotherapy and increased 6 mo after chemotherapy	Negative correlation of decreased ADMN FC changes with increased DST score changes
Zheng 2021	High	DMN	Increased ALFF pre-CTX and post-CTX: left inferior temporal gyrus, right middle temporal gyrus, left middle temporal, upper gyrus, and bilateral precuneus	NSD or correlations
Hu 2020	High	CEN	At 3–6 mo: reductions in static FC between right DLPFC and bilateral superior frontal gyrus, left middle frontal gyrus, or right medial cingulate gyrus and between left DLPFC and right middle frontal gyrus. Decreased static FC between the right DLPFC and left superior frontal gyrus and increased static FC between the left DLPFC and right insula. Reduced dynamic FC variability between right DLPFC and right superior parietal lobule. Decreased dynamic FC variability between right DLPFC and right precuneus, left DLPFC and right inferior frontal gyrus or left inferior temporal gyrus	Negative correlation of decreased dynamic FC of the right DLPFC to the left superior frontal gyrus with MoCA scores
Jung 2017	High	CEN	Greater spatial variance in task activation in CEN at 1 y (vs HC). Overall verbal working memory task scores at 1 y worse in CTX than HC. CTX performed worse across all levels of task demand	At 1 y, VWMT performance and CEN spatial variance were each independently predicted by CTX treatment and their respective baseline values, while cognitive complaints were predicted by baseline level, physical symptoms and worry

Continued

Table 5 Relationship Between Connectivity Alterations and Cognitive Changes in Chemotherapy-Treated Patients With Cancer in High Evidence Studies *(continued)*

Study	Study quality	WM, GMD, RSNs	CTX group connectivity changes	Association of connectivity with test performance in CTX group
Lopez Zunini 2013	High	Activation	Decreased activation in bilateral insulae, left inferior orbitofrontal cortex, and bilateral middle temporal gyri	Higher anxiety scores correlated with more activity in the right medial frontal gyrus and higher fatigue scores correlated with more activity in the right medial frontal gyrus and left hippocampus
Menning 2017	High	Activation	Increased activation in bilateral inferior parietal cortex and precuneus extending to superior parietal cortex with increasing task load (vs non-CTX)	Increased parietal activation with increasing executive functioning task load and accompanied by worse physical functioning, higher levels of fatigue, and more cognitive complaints

Abbreviations: ADMN = anterior DMN; ALFF = amplitude of low frequency fluctuation; AVLT = auditory-verbal learning test; CEN = central executive network; CTX = chemotherapy; DAN = dorsal attention network; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; DST = digit span test; FA = fractional anisotropy; fALFF = fractional amplitude of low frequency fluctuation; FC = functional connectivity; GMD = gray matter density; HC = healthy controls; LFPN = left frontoparietal network; MD = mean diffusivity; MoCA = montreal cognitive assessment; NAA = N-acetylaspartate; NSD = no significant differences; OCEBM = Oxford centre for evidence-based medicine; PDMN = posterior DMN; QSR = questionnaire of self-representations; RD = radial diffusivity; ReHo = regional homogeneity; RFPN = right frontoparietal network; RSN = resting-state network; SCWT = stroop color and word test; SDBOLD = SD of blood oxygen level dependent signal; SDS = Self-Rating Depression Scale; SMN = sensorimotor network; SRN = self-referential network; VWMT = verbal memory working task; WM = white matter.
This table presents high-evidence studies reporting structural (gray matter density, white matter integrity) and functional (activation, resting-state networks) connectivity alterations in chemotherapy-treated (CTX) patients, along with corresponding cognitive or psychological changes. Specific resting-state networks, such as the default mode network, dorsal attention network, and central executive network, are indicated when applicable. All studies in this table are prospective and OCEBM evidence level 2.

particular, the DLPFC showed correlations between the strength of its FC and tests of executive function.[36,41,42] In 1 study, attention impairment in CTX patients correlated with the low connectivity of components of the DMN. Functional connectivity of the ventromedial prefrontal cortex and retrosplenium in the medial temporal lobe subsystem significantly correlated with response time in attention tests.[43] Alterations in the CEN correlated with impairments in executive function[42] and greater subjective executive dysfunction and memory complaints correlated with lower connectivity in the anterior cingulate and insula in CTX groups.[44] Decreased FC between the posterior and anterior cingulate in patients with post-CTX lung cancer was positively correlated with reduced Montreal Cognitive Assessment scores in 1 study,[45] and 1 breast cancer study demonstrated an association between DMN dysfunction and signs of accelerated aging in patients with CTX-treated older cancer.[46]

Discussion

A variety of imaging techniques have been used to assess CRCI-associated neural changes, with the goals of characterizing anatomical and structural changes in white and gray brain matter, assessing connectivity alterations within and between brain networks, or quantifying disruptions in the brain's metabolic environment. MRI, because of its availability, noninvasiveness, and versatility, is an important tool in this research. Structural MRI allows for assessment of the brain's physical structure and offers a high level of anatomical and spatial resolution, including gray matter, WM, and CSF.[47] fMRI is increasingly used to measure brain activity, tracking spontaneous fluctuations in blood oxygen level-dependent signals over time to observe differential stimulation of brain regions and networks.[48]

Several mechanisms have been proposed to explain observed CTX-induced structural and functional connectomic changes. Chemotherapy is believed to trigger neuroinflammation through increased cellular death and oxidative damage, which disrupts microglial activity. Hormonal changes, disruptions to the blood-brain barrier, DNA damage, telomere shortening, increased cytokine release, and gene alterations related to neural repair are other proposed mechanisms by which CTX treatment can result in cognitive impairment.[49]

This systematic review identified several broad themes related to CRCI and brain connectivity changes. Cognitive impairments in domains such as memory, processing speed, and attention were consistently reported across many studies, suggesting these areas may be particularly vulnerable to CTX effects. However, the evidence linking these cognitive deficits to specific alterations in brain connectivity is inconsistent, which may be due to differences in study design, neuroimaging techniques, and patient populations. Moreover, the variability observed across studies may be influenced by the different chemotherapeutic agents and treatment regimens used. Different agents have varying neurotoxic profiles, which could lead to variations in the extent of brain connectivity changes observed.[50] In addition, the intensity, duration, and combination of CTX regimens could further influence cognitive outcomes. The timing of assessments post-treatment also plays a critical role because cognitive function may change depending on whether the patient is assessed immediately after CTX or several months later. Furthermore, interactions with other

treatments like radiation or surgery could amplify cognitive deficits, complicating the interpretation of results.

To strengthen the evidence in this area, future research should prioritize the standardization of neuroimaging protocols, cognitive assessments, and study designs to reduce variability and improve the comparability of findings across studies. Larger, multicenter studies with diverse patient populations should be conducted to enhance the generalizability of results. Longitudinal studies are also needed to observe changes over time and differentiate between transient and persistent cognitive impairments. In an attempt to understand the association between CRCI and connectivity changes, cognitive function should be a key endpoint in clinical trials. Standardized cognitive assessments should be included and clinical trials should potentially explore interventions aimed at cognitive rehabilitation, which could become a standard part of postchemotherapy care. In addition to traditional survival metrics and cognitive function, trials should consider quality of life as an important endpoint to provide a more holistic view of patient outcomes.

Notably, 13 studies in this review reported structural and FC changes in patients with cancer treated with and without CTX. Although the directionality (i.e., increased or decreased connectivity) of these changes often differed between groups, both groups of patients with cancer exhibited changes in key connectivity metrics. Table 3 outlines how the differences in the number of studies reporting intergroup connectivity changes frequently varies by only 1 study per metric. This suggests that, while studies may point to some effects of CTX on connectivity metrics, the changes do not seem drastically different between CTX and non-CTX groups. While there is a potential trend in this small subset of 13 studies toward CTX affecting brain connectivity, this should be interpreted with caution because of the reportedly minor differences. That said, it is possible that the directionality of connectivity changes may result in more frequent cognitive impairments in patients with cancer treated with CTX. Therefore, comparison groups of patients with cancer not receiving CTX may be equally as important as healthy controls because their inclusion may control for the effects of cancer itself, which may independently influence brain function.

This systematic review suggests that CTX is linked to various structural and functional brain alterations that may contribute to cognitive impairment. However, the evidence remains inconsistent, particularly in the associations between connectivity changes and cognitive outcomes. Further research, particularly in the form of high evidence level studies, is needed to clarify and understand the associations between connectivity changes and cognitive/psychological performance postchemotherapy.

While this review attempts to provide a comprehensive overview of current literature, there are several limitations. First, PubMed, Web of Science, and Embase were the only databases queried in this review, which may not have captured all available studies. Secondly, only English articles were considered. Third, most included studies were cross-sectional in design, making it difficult to draw any causal associations between the clinical presentation of patients treated with CTX and any underlying connectivity changes. In addition, the reported results in most of these studies were not easily generalizable because the studies were mostly cross-sectional, primarily evaluated patients with breast cancer and were not methodologically consistent.

These studies may also be subject to confounders such as differences in the type of scanner used, motion artifact, patient age and sex, and patient comorbidities, making them difficult to compare directly. Moreover, it is difficult to draw definitive conclusions when there is a lack of consistency in the chemotherapeutic agents used, the type of cancer being treated, and the small sample size of CTX-treated patients in each study, with the largest CTX cohort reported by Koppelmans et al., 2014 (n = 187).

This systematic review indicates that CTX is linked to various structural and functional brain alterations, which may contribute to cognitive impairments experienced by patients posttreatment. However, the evidence is not conclusive. Most studies included were cross-sectional, and 45% of high evidence level studies did not find significant associations between CTX and cognitive impairments.

Future research should consider adopting a standardized methodology across studies to reduce variability and improve comparability. Specifically, we recommend the use of a core set of neuroimaging protocols and cognitive assessments that are uniformly applied across studies. This could involve adopting widely accepted imaging modalities such as fMRI and DTI alongside standardized cognitive testing batteries. In addition, research should focus on conducting large, longitudinal studies that follow patients from pretreatment through long-term posttreatment periods, allowing researchers to differentiate between transient and persistent cognitive impairments and better understand the temporal relationship between CTX and changes in brain connectivity. Finally, researchers should consider using mixed-methods approaches that combine quantitative neuroimaging and cognitive data with qualitative patient-reported outcomes to provide an understanding of CRCI and its effects on quality of life.

Author Contributions

S. Leskinen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Alsalek: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. R. Galvez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept

or design; analysis or interpretation of data. F.C. Ononogbu-Uche: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. H.A. Shah: drafting/revision of the manuscript for content, including medical writing for content. M. Vojnic: drafting/revision of the manuscript for content, including medical writing for content. R.S. D'Amico: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* June 20, 2024. Accepted in final form September 25, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Rebecca Burch, MD.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33. doi:10.3322/caac.21654
2. Anand U, Dey A, Chandel AKS, et al. Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes Dis*. 2023;10(4):1367-1401. doi:10.1016/j.gendis.2022.02.007
3. Bernstein LJ, Edelstein K, Sharma A, Alain C. Chemo-brain: an activation likelihood estimation meta-analysis of functional magnetic resonance imaging studies. *Neurosci Biobehav Rev*. 2021;130:314-325. doi:10.1016/j.neubiorev.2021.08.024
4. Rao V, Bhushan R, Kumari P, Cheruku SP, Ravichandiran V, Kumar N. Chemobrain: a review on mechanistic insight, targets and treatments. *Adv Cancer Res*. 2022;155:29-76. doi:10.1016/bs.acr.2022.04.001
5. Behrens TE, Sporns O. Human connectomics. *Curr Opin Neurobiol*. 2012;22(1):144-153. doi:10.1016/j.conb.2011.08.005
6. Kesler SR, Petersen ML, Rao V, Harrison RA, Palesh O. Functional connectome biotypes of chemotherapy-related cognitive impairment. *J Cancer Surviv*. 2020;14(4):483-493. doi:10.1007/s11764-020-00863-1
7. Robinson KE, Kuttesch JF, Champion JE, et al. A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatr Blood Cancer*. 2010;55(3):525-531. doi:10.1002/pbc.22568
8. Simó M, Root JC, Vaquero L, et al. Cognitive and brain structural changes in a lung cancer population. *J Thorac Oncol*. 2015;10(1):38-45. doi:10.1097/JTO.0000000000000345
9. Abraham J, Haut MW, Moran MT, Filburn S, Lemiuex S, Kuwabara H. Adjuvant chemotherapy for breast cancer: effects on cerebral white matter seen in diffusion tensor imaging. *Clin Breast Cancer*. 2008;8(1):88-91. doi:10.3816/CBC.2008.n.007
10. Menning S, de Ruiter MB, Veltman DJ, et al. Changes in brain white matter integrity after systemic treatment for breast cancer: a prospective longitudinal study. *Brain Imaging Behav*. 2018;12(2):324-334. doi:10.1007/s11682-017-9695-x
11. Tong T, Lu H, Zong J, Lv Q, Chu X. Chemotherapy-related cognitive impairment in patients with breast cancer based on MRS and DTI analysis. *Breast Cancer*. 2020;27(5):893-902. doi:10.1007/s12282-020-01094-z
12. Deprez S, Amant F, Yigit R, et al. Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. *Hum Brain Mapp*. 2011;32(3):480-493. doi:10.1002/hbm.21033
13. Deprez S, Amant F, Smeets A, et al. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. *J Clin Oncol*. 2012;30(3):274-281. doi:10.1200/JCO.2011.36.8571
14. de Ruiter MB, Reneman L, Boogerd W, et al. Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: converging results from multimodal magnetic resonance imaging. *Hum Brain Mapp*. 2012;33(12):2971-2983. doi:10.1002/hbm.21422
15. Chen BT, Ye N, Wong CW, et al. Effects of chemotherapy on aging white matter microstructure: a longitudinal diffusion tensor imaging study. *J Geriatr Oncol*. 2020;11(2):290-296. doi:10.1016/j.jgo.2019.09.016
16. Kesler SR, Bennett FC, Mahaffey ML, Spiegel D. Regional brain activation during verbal declarative memory in metastatic breast cancer. *Clin Cancer Res*. 2009;15(21):6665-6673. doi:10.1158/1078-0432.CCR-09-1227
17. Menning S, de Ruiter MB, Veltman DJ, et al. Changes in brain activation in breast cancer patients depend on cognitive domain and treatment type. *PLoS One*. 2017;12(3):e0171724. doi:10.1371/journal.pone.0171724
18. Pergolizzi D, Root JC, Pan H, et al. Episodic memory for visual scenes suggests compensatory brain activity in breast cancer patients: a prospective longitudinal fMRI study. *Brain Imaging Behav*. 2019;13(6):1674-1688. doi:10.1007/s11682-019-00038-2
19. Jung MS, Zhang M, Askren MK, et al. Cognitive dysfunction and symptom burden in women treated for breast cancer: a prospective behavioral and fMRI analysis. *Brain Imaging Behav*. 2017;11(1):86-97. doi:10.1007/s11682-016-9507-8
20. López Zunini RA, Scherling C, Wallis N, et al. Differences in verbal memory retrieval in breast cancer chemotherapy patients compared to healthy controls: a prospective fMRI study. *Brain Imaging Behav*. 2013;7(4):460-477. doi:10.1007/s11682-012-9213-0
21. Conroy SK, McDonald BC, Smith DJ, et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. *Breast Cancer Res Treat*. 2013;137(2):493-502. doi:10.1007/s10549-012-2385-x
22. Wang L, Apple AC, Schroeder MP, et al. Reduced prefrontal activation during working and long-term memory tasks and impaired patient-reported cognition among cancer survivors postchemotherapy compared with healthy controls. *Cancer*. 2016;122(2):258-268. doi:10.1002/cncr.29737
23. McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Alterations in brain activation during working memory processing associated with breast cancer and treatment: a prospective functional magnetic resonance imaging study. *J Clin Oncol*. 2012;30(20):2500-2508. doi:10.1200/JCO.2011.38.5674
24. de Ruiter MB, Reneman L, Boogerd W, et al. Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. *Hum Brain Mapp*. 2011;32(8):1206-1219. doi:10.1002/hbm.21102
25. Bromis K, Kakkos I, Gkiatis K, Karanasiou IS, Matsopoulos GK. Brain functional connectivity in small cell lung cancer population after chemotherapy treatment: an ICA fMRI Study. *J Phys Conf Ser*. 2017;931:012041. doi:10.1088/1742-6596/931/1/012041
26. You J, Hu L, Zhang Y, et al. Altered dynamic neural activity in the default mode network in lung cancer patients after chemotherapy. *Med Sci Monit*. 2020;26:e921700. doi:10.12659/MSM.921700
27. Zheng F, Cao P, Zhou J, Li C, Norris J. Study on neurologic and cognitive dysfunction in breast cancer patients undergoing chemotherapy with resting state fMRI. *World Neurosurg*. 2021;149:388-396. doi:10.1016/j.wneu.2020.10.088
28. Dumas JA, Makarewicz J, Schaubhut GJ, et al. Chemotherapy altered brain functional connectivity in women with breast cancer: a pilot study. *Brain Imaging Behav*. 2013;7(4):524-532. doi:10.1007/s11682-013-9244-1
29. Feng Y, Wang YF, Zheng LJ, Shi Z, Huang W, Zhang LJ. Network-level functional connectivity alterations in chemotherapy treated breast cancer patients: a longitudinal resting state functional MRI study. *Cancer Imaging*. 2020;20(1):73. doi:10.1186/s40644-020-00355-6
30. Abraham J, Haut MW, Moran MT, Filburn S, Lemiuex S, Kuwabara H. Adjuvant chemotherapy for breast cancer: effects on cerebral white matter seen in diffusion tensor imaging. *Clin Breast Cancer*. 2008;8(1):88-91. doi:10.3816/CBC.2008.n.007
31. Li X, Chen HJ, Lv Y, et al. Diminished gray matter density mediates chemotherapy dosage-related cognitive impairment in breast cancer patients. *Sci Rep*. 2018;8(1):13801. doi:10.1038/s41598-018-32257-w
32. Correa DD, Root JC, Kryza-Lacombe M, et al. Brain structure and function in patients with ovarian cancer treated with first-line chemotherapy: a pilot study. *Brain Imaging Behav*. 2017;11(6):1652-1663. doi:10.1007/s11682-016-9608-4
33. Kesler SR, Kent JS, O'Hara R. Prefrontal cortex and executive function impairments in primary breast cancer. *Arch Neurol*. 2011;68(11):1447-1453. doi:10.1001/archneurol.2011.245
34. Miao H, Li J, Hu S, et al. Long-term cognitive impairment of breast cancer patients after chemotherapy: a functional MRI study. *Eur J Radiol*. 2016;85(6):1053-1057. doi:10.1016/j.ejrad.2016.03.011
35. Chen BT, Jin T, Patel SK, et al. Intrinsic brain activity changes associated with adjuvant chemotherapy in older women with breast cancer: a pilot longitudinal study. *Breast Cancer Res Treat*. 2019;176(1):181-189. doi:10.1007/s10549-019-05230-y
36. Park HY, Lee H, Sohn J, An SK, Namkoong K, Lee E. Increased resting-state cerebellar-cortical connectivity in breast cancer survivors with cognitive complaints after chemotherapy. *Scientific Rep*. 2021;11(1):12105. doi:10.1038/s41598-021-91447-1
37. Piccirillo JF, Hardin FM, Nicklaus J, et al. Cognitive impairment after chemotherapy related to atypical network architecture for executive control. *Oncology*. 2015;88(6):360-368. doi:10.1159/000370117
38. Perrier J, Joue G, Desgranges B, et al. Self-referential processes and resting-state connectivity in breast cancer patients before and 1 year after chemotherapy. *Eur J Neurosci*. 2022;55(2):624-636. doi:10.1111/ejn.15587
39. Stouten-Kemperman MM, De Ruiter MB, Boogerd W, et al. Brain hyperconnectivity >10 Years after cisplatin-based chemotherapy for testicular cancer. *Brain Connect*. 2018;8(7):398-406. doi:10.1089/brain.2017.0569
40. Tao L, Lin H, Yan Y, et al. Impairment of the executive function in breast cancer patients receiving chemotherapy treatment: a functional MRI study. *Eur J Cancer Care*. 2017;26(6):e12553. doi:10.1111/ecc.12553

41. Hu Y, Liu D, Deng Y, et al. Changes in degree centrality and functional connectivity after the first cycle of neoadjuvant chemotherapy in newly diagnosed breast cancer: a longitudinal study. *Dis Markers*. 2022;2022:8270100. doi:10.1155/2022/8270100
42. Wang L, Yan Y, Wang X, et al. Executive function alternations of breast cancer patients after chemotherapy: evidence from resting-state functional MRI. *Acad Radiol*. 2016;23(10):1264-1270. doi:10.1016/j.acra.2016.05.014
43. Miao H, Chen X, Yan Y, et al. Functional connectivity change of brain default mode network in breast cancer patients after chemotherapy. *Neuroradiology*. 2016;58(9):921-928. doi:10.1007/s00234-016-1708-8
44. Henneghan AM, Kesler SR. Subjective cancer-related cognitive impairments and salience network connectivity in breast cancer survivors. *J Cancer Surviv*. 2023;17(4):967-973. doi:10.1007/s11764-022-01307-8
45. Zhang Y, Chen YC, Hu L, et al. Chemotherapy-induced functional changes of the default mode network in patients with lung cancer. *Brain Imaging Behav*. 2020;14(3):847-856. doi:10.1007/s11682-018-0030-y
46. Chen BT, Chen Z, Patel SK, et al. Effect of chemotherapy on default mode network connectivity in older women with breast cancer. *Brain Imaging Behav*. 2022;16(1):43-53. doi:10.1007/s11682-021-00475-y
47. Symms M, Jager HR, Schmierer K, Yousry TA. A review of structural magnetic resonance neuroimaging. *J Neurol Neurosurg Psychiatry*. 2004;75(9):1235-1244. doi:10.1136/jnnp.2003.032714
48. Logothetis NK. The underpinnings of the BOLD functional magnetic resonance imaging signal. *J Neurosci*. 2003;23(10):3963-3971. doi:10.1523/JNEUROSCI.23-10-03963.2003
49. Ren X, Boriero D, Chaiswing L, Bondada S, St Clair DK, Butterfield DA. Plausible biochemical mechanisms of chemotherapy-induced cognitive impairment ("chemobrain"), a condition that significantly impairs the quality of life of many cancer survivors. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(6):1088-1097. doi:10.1016/j.bbadis.2019.02.007
50. Amidi A, Hosseini SMH, Leemans A, et al. Changes in brain structural networks and cognitive functions in testicular cancer patients receiving cisplatin-based chemotherapy. *J Natl Cancer Inst*. 2017;109(12). doi:10.1093/jnci/djx085