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Neuroimaging, Cancer, and Cognition: State of the Knowledge

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Abstract

Objectives—To review neuroimaging research concerning cancer- and treatment-related changes in brain structure and function, clinical perspectives, and future directions.**Data Sources**—Peer-reviewed literature**Conclusion**—Cancer and chemotherapy are associated with cerebral structural and functional alterations in breast cancer patients which may persist for years; many of these changes are correlated with cognitive complaints or performance. In other cancers there is some evidence that metabolism is altered by cancer, but more research is needed.**Implications for Nursing Practice**—Understanding the role of neuroimaging is important to identify the basis of cognitive changes associated with cancer and cancer treatment.

Keywords

cancer; cognition; neuroimaging; review

Multiple neuroimaging techniques have been applied in studies of cancer- and chemotherapy treatment-related cognitive dysfunction, with promising results. Magnetic resonance imaging (MRI) most commonly is employed. MRI uses radio frequencies to manipulate magnetization of various types of nuclei in the body, with the resulting signatures used to produce detailed 2- or 3-dimensional images.^{1,2} This technology has been adapted to measure a number of different factors, including brain gray matter (GM), white matter (WM), and neural activity using functional MRI (fMRI). WM structure and directional diffusion, or ‘fractional anisotropy’ (FA), is measured through diffusion tensor imaging (DTI) of magnetized cerebral water flow.^{3,4} Brain activation is obtained using magnetized hemoglobin to observe oxygenated blood flow; increased blood flow to active areas is

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measured during tasks, and fMRI has been reliably correlated with neural activity.⁵⁻⁷ Proton MR spectroscopy (1H-MRS) also uses magnetic resonance technology to measure levels of brain metabolites and neurochemical changes.⁸ MRI techniques have the advantage of being non-invasive and do not require ionizing radiation, permitting multiple measurements and longitudinal studies. Positron emission tomography (PET) is another technique that has been employed to measure brain activity and metabolism using an injected radioactive tracer coupled to a bioactive molecule; two common tracers which will be discussed are [O-15], which measures blood flow, and [F-18] Fluorodeoxyglucose (FDG), which measures metabolism.⁹⁻¹¹ These techniques can be used to investigate neurophysiological changes and may help explain the mechanisms of cognitive dysfunction in cancer patients.

The purpose of this research brief is to review the current literature on neuroimaging studies of cancer and chemotherapy-induced cerebral alterations, and to provide perspective on the state of research and future directions. Our primary goal is to review and synthesize the evidence regarding the impact of non-central nervous system cancer and related treatment on brain structure and function. Treatments administered for cancers in the central nervous system (CNS) and lymphatic systems operate under different parameters and goals and are beyond the scope of this review.¹² Findings from imaging studies have the potential to identify causal mechanisms and possible therapeutic directions for cancer and treatment-related cognitive dysfunction.

Overview of Findings

We reviewed 35 neuroimaging studies. The overwhelming majority of the work in this area has been focused on breast cancer (BC) patients, with 27 BC studies¹³⁻⁴⁰ and only eight studies in other cancers.⁴¹⁻⁴⁸ In the BC studies, we noted that 18 studies were focused on survivors,^{14-17,19-21,23-30,38-40} three were pre-treatment cancer studies,^{18,36,37} and six were longitudinal studies in which women were followed pre- and post-treatment.^{13,22,31-34} These studies are grouped by methodology and information is provided regarding authors, cohorts, methods, and results in Tables 1-3. The majority of non-BC studies (see Table 4) were focused on the association of metabolism with psychological factors or cancer. In summary, research to date has been focused on the cognitive effects of BC treatment, likely due to the large pool of survivors with cognitive concerns.^{35,40,49,50} This brief provides an overview including all types of neuroimaging studies on multiple types of cancer.

Breast Cancer Survivor Studies

Neuroimaging studies began with a focus on survivors treated with chemotherapy. Initial findings on this topic presented in 2003 indicated that chemotherapy treatment was associated with structural changes in gray matter (GM), white matter (WM) loss, and abnormal regional cerebral metabolism measured by PET.^{40,51,52} The focus of these BC studies (Table 1) was on patients treated with chemotherapy (C+). All studies included a C+ category, and 15 included healthy controls (HC).^{14-17,19,23-30,38,40} However, only seven studies included untreated survivors (C-), so the findings are limited since in most studies differentiation between changes caused by treatment or cancer was not possible.^{20,21,23,26,28,38,39}

The major endpoints of these studies were cerebral structural and activation changes. GM and WM damage consistently were reported in survivors except for Yoshikawa et al. This discrepancy may be explained by unique cohort characteristics such as ethnicity, since the majority of studies were conducted with Caucasian patients and this study only included Japanese individuals.³⁹ Authors of three studies reported association of these changes with increased cognitive complaints or decreased neuropsychological test performance.^{16,19,23} Results from all six functional studies demonstrated activation or metabolic changes in

survivors.^{19,21,24,27,28,38} The direction of activation change seems to be task-dependent. In two studies activation change was found to be correlated with increased cognitive complaints.^{19,28} Importantly, in two studies de Ruiter et al. found treatment-related cognitive alterations almost a decade after treatment, accompanied by lower neuropsychological test performance and increased cognitive complaints.^{20,21} Koppelmans et al. conducted two studies with a very large survivor cohort over 20 years post-treatment. Findings included decreased brain volume, GM, and decreased WM integrity with increasing time since treatment, supporting the idea that BC, treatment, or both are responsible for long-term possibly deleterious cognitive changes.^{29,30} Results from all but one of these studies support the association of chemotherapy treatment with some measure of cognitive structural or function alteration which could lead to cognitive dysfunction. The majority of these findings are accompanied by neuropsychological testing deficits, increased self-reported cognitive complaints, or both, indicating the functional relevance of these measures. However, more work is needed to discern which measures are specific to treatment and which to cancer.

Pre-Chemotherapy Breast Cancer Studies

Prompted by the need to discriminate between effects of BC and treatment, three imaging studies were designed specifically to examine the influence of BC on cognition.^{18,36,37} BC patients were examined before treatment and compared to HC with fMRI during neuropsychological tasks. Activation decrease was observed for patients during response inhibition and working memory tasks, while activation increase was observed during a visuospatial task. Interestingly, two studies by Scherling et al. were performed in the same cohort using different tasks and found evidence that activation increase or decrease may be dependent on the type of task. These activation changes were not associated with test performance changes, suggesting that they may be compensatory.^{36,37} This lack of association suggests that while BC does appear to influence cognitive activation, the effects may vary depending on the cognitive process being assessed. Activation also may be a more sensitive measure of change than test performance.

Longitudinal Breast Cancer Treatment Studies

The existing longitudinal studies particularly are helpful in differentiating cancer and chemotherapy effects, especially as four of the six studies reviewed included C- and HC.^{22,31-34} Pre-treatment measures for all patients also allow discrimination of cancer and chemotherapy effects over time. Results of all six studies demonstrated some cerebral changes in cancer patients compared to controls, and results of the five studies with C- controls indicated that some of these changes are specifically attributable to chemotherapy, while others appear to occur in cancer patients regardless of treatment. These findings suggest that while cancer patients experience cognitive alterations, chemotherapy may have independent effects. Thus C+ patients may experience increased alterations compared to C- patients, and may be at increased risk for cognitive sequelae. Two studies were designed to investigate effects of cancer and chemotherapy more than four months post-treatment with C+, C-, and HC groups. Findings included independent cancer and treatment-related activation and GM changes post-treatment.^{33,34} At one year post-treatment, some activation changes still were observed in C+ and C-, and GM decrease was not fully recovered in C+ patients, indicating that structural and functional changes can persist for significant periods of time.

Non-BC Studies

As stated previously, there is a dearth of research on this topic in non-BC cancers. Additionally, of the eight studies found, three studies were focused on the correlation of

metabolism with psychological factors instead of cognitive factors.⁴¹⁻⁴⁸ However, these studies are still informative given that depression and cognitive complaints previously have been linked.⁵³ These findings provide indirect evidence for association of brain metabolism with cognitive complaints. Interestingly, results of a study in a lung cancer cohort indicated that patients had increased metabolism pre-treatment, suggesting that cancer may have a transitory metabolic effect on the brain in lung cancer.⁴⁷ Results from another study of lung cancer indicated that patients had altered neurochemistry pre-treatment, further supporting the hypothesis that lung cancer may alter cerebral activity.⁴⁸

Six studies were conducted in a mixed cancer population. All were limited by the assumption that the cancer types included in the studies affect the brain in a similar manner, which may not be true.⁴¹⁻⁴⁶ Only one study was designed to investigate the effect of chemotherapy treatment on metabolism. Decreased metabolism in C+ patients was found, demonstrating that other cancer populations do experience treatment changes.⁴⁵ Three studies in mixed cohorts of treated and untreated cancer patients found decreased metabolism associated with cancer, supporting the possibility of cancer-induced cerebral alterations in non-BC patients.⁴⁴⁻⁴⁶ However, in seven of the eight studies only FDG-PET imaging was used. Clearly, more research is needed to investigate other imaging types in these populations. Future work also should include longitudinal studies with C+, C-, and HC groups to identify cancer and chemotherapy-specific changes, and should control for cancer type, or focus on one cancer.

Clinical Implications and Future Research

Oncology nurses and other healthcare providers should understand the role neuroimaging can play in identifying cognitive changes associated with cancer and cancer treatment, as well as the impact of these changes on social relationships, everyday functioning and work ability.⁵⁴ Directions for future neuroimaging research are: (1) to elucidate cancer and treatment-related changes in more diverse cohorts; (2) to utilize a range of imaging methodologies, as most studies to date have been focused solely on MRI and fMRI; and (3) to utilize neuroimaging in interventional cognitive research to establish efficacy as well as elucidate therapeutic mechanisms of action.

Conclusion

Results from neuroimaging studies in BC cohorts have provided solid evidence supporting a variety of cerebral structural and functional alterations associated with cancer and chemotherapy treatment. Evidence from BC survivors suggests that some of these changes persist for years. Little imaging research has been conducted in other cancer types; however, preliminary studies support cancer-related cerebral metabolic changes. More research is needed to clarify the individual roles of cancer and treatment-related changes, especially in non-BC populations.

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Table 1

Breast Cancer Survivor Neuroimaging Studies

Study	Cohort	PCI ^a	Method	Results
Saykin et al. ⁴⁰	12 C+ ^b , 12 H	>5Y	sMRI	C+: WM and GM
Yoshikawa et al. ³⁹	44 C+, 31 C-	>3Y	sMRI, NP	C+: No treatment associations
Ferguson et al. ²⁴	1 C+, 1 H	22M	s/fMRI, NP, SR	C+: SR, WM damage, WMem activation
Silverman et al. ³⁸	16 C+, 5 C-, 13 H	5-10Y	O-15 & FDG PET, NP	C+: altered CBF during memory task; resting metabolism correlated with task performance
Inagaki et al. ²⁶	1Y: 51 C+, 54 C-, 55 H; 3Y: 73 C+, 59 C-, 37 H	1Y and 3Y	sMRI, NP	1Y C+: GM and WM vs. C-, not vs. H. 3Y C+: no treatment association with GM/WM
Abraham et al. ¹⁵	10 C+, 9 H	22M	DTI, NP	C+: PS, FA
Kesler et al. ²⁷	14 C+, 14 H	>6M	fMRI	C+: activation encoding, recall in VDM task
Kesler et al. ²⁸	25 C+, 19 C-, 18 H	5Y	fMRI, NP, SR	C+ & C-: activation for EF task C+: SR complaints, NP errors, PS, activation correlated with SR, disease severity
de Ruiter et al. ²¹	19 C+, 15 C-	>9Y	fMRI, NP	HD C+: activation for EF and EMem tasks, NP
Deprez et al. ²³	17 C+, 10 C-, 18 H	2-4M	DTI, NP, SR	C+: FA, MD vs. C- and H; FA correlated with attention, PS, SR
Bergouignan et al. ¹⁶	16 C+, 21 H	18-36M	sMRI, NP	C+: GM, NP; GM correlated with NP
Kesler et al. ¹⁴	42 C+, 35 H	4.8Y	sMRI, INF, NP	C+: GM, NP, INF; GM correlated with INF
Koppelmans et al. ²⁹	184 C+, 368 H	21Y	sMRI	C+: TBV, GM
Koppelmans et al. ³⁰	187C+, 374 H	21Y	DTI	C+: WM integrity correlated with time since treatment; no change vs. H
Hosseini et al. ²⁵	37 C+, 38 H	4.5Y	sMRI	C+: GM connectivity, organization, integration
Bruno et al. ¹⁷	34 C+, 27 H	5.35Y	fMRI, SR	C+: SR, global cluster, nodal degree, hubs
de Ruiter et al. ²⁰	17 HD C+, 15 C-	>9Y	DTI, sMRI, NP, SR	C+: SR, NP, GM, focal FA; MD correlated with neural markers
Conroy et al. ¹⁹	24 C+, 23 H	3-10Y	s/fMRI, NP, SR, Comet	C+: GM, WMem activation, NP; GM correlated with PCI, NP, activation correlated with PCI, SR, OD

PCI=post-chemotherapy interval, C+=survivors treated with chemotherapy, C-=survivors not treated with chemotherapy, H=healthy controls, Y=year, M=month, HD=high dose, sMRI=structural MRI, fMRI=functional MRI, DTI=diffusion tensor imaging, FDG-PET=[F-18] Fluorodeoxyglucose positron emission tomography, Comet=assay of oxidative DNA damage, oxidative DNA damage=OD, NP=neuropsychological testing, SR=self-report cognitive complaints assessment, =decrease, =increase, GM=gray matter, WM=white matter, WMem=working memory, CBF=cerebral blood flow, PS=processing speed, FA=fractional anisotropy, MD=mean diffusivity, VDM=verbal declarative memory task, EF=executive function, EMem=episodic memory, TBV=total brain volume

^aWhen one number is listed, this is the average length of time post-treatment

^b10 breast cancer, 2 lymphoma survivors

Table 2

Pre-Chemotherapy Breast Cancer Neuroimaging Studies

Study	Cohort	Method	Results
Cimprich et al. ¹⁸	10 PC, 9 H	fMRI	PC: speed, accuracy for verbal WMem task, activation
Scherling et al. ³⁶	23 PC, 23 H	fMRI	PC: activation during VS task, reaction time, errors
Scherling et al. ³⁷	23 PC, 23 H	fMRI	PC: activation during RI task, no performance change

PC=cancer patients who have not yet received chemotherapy, H=healthy controls, fMRI=functional MRI, =decrease, =increase, WMem=working memory, VS=visuospatial, RI=response inhibition

Table 3

Longitudinal Breast Cancer Neuroimaging Studies

Study	Cohort	Measures	Method	Results
McDonald et al. ³²	17 C+, 12 C-, 18 H	BL, 1M, 1Y	sMRI	C+ & C-: GM from BL to 1M C+: some changes persist at 1Y
McDonald et al. ³³	16 C+, 12 C-, 15 H	BL, 1M, 1Y	fMRI	C+&C-: frontal, left parietal BL WMem activation, 1M frontal activation, 1Y partial recovery C+: frontal activation at BL, 1M, 1Y
McDonald et al. ³⁴	27 C+, 28 C-, 24 H	BL, 1M	sMRI, SR	C+: GM at 1M; SR correlated with GM
Ganz et al. ¹³	49 C+, 44 C-	8.7MD, 14.7MD, 20.7MD	SR, NP, FDG-PET, INF	C+: 8.7MD SR, INF, INF correlated to inferior frontal metabolism; longitudinal INF correlated to SR
Deprez et al. ²²	34 C+, 16 C-, 19 H	BL, 3-4M	DTI, NP	C+: NP at 1M vs. BL; NP correlated with FA
Lopez Zunini et al. ³¹	21 C+, 21 H	BL, 1M	fMRI, NP	C+: VMem activation at BL, 1M vs. BL

C+=survivors treated with chemotherapy, C-=survivors not treated with chemotherapy, H=healthy controls, BL=baseline (pre-chemotherapy), M=month post-treatment, MD=month post-diagnosis, Y=year post-treatment, sMRI=structural MRI, fMRI=functional MRI, SR=self-report cognitive assessment, FDG-PET=[F-18] Fluorodeoxyglucose positron emission tomography, INF=inflammatory markers, DTI=diffusion tensor imaging, NP=neuropsychological testing, =decrease, =increase, GM=gray matter, WMem=working memory, FA=fractional anisotropy, VMem=verbal memory

Table 4

Non-CNS, Non-Breast Cancer Neuroimaging Studies

Study	Cancer	Cohort	Design	Method	Results
Tashiro et al. ⁴⁶	Various	19 PC, 17 H	Cross-section	FDG-PET	Cancer: metabolism
Tashiro et al. ⁴⁴	Various	1 PC, 19 C+/-, 10 H	Cross-section	FDG-PET, SR	Cancer: metabolism
Tashiro et al. ⁴⁵	Various	2 PC, 7 C+, 12 C-, 10 H	Cross-section	FDG-PET, SR	Cancer: metabolism; metabolism correlated with depression C+: posterior metabolism
Tashiro et al. ⁴²	Various	4 PC, 3 C-, 1 C+	Cross-section	FDG-PET, NKA, SR	Cancer: Metabolism, NKA, and anxiety correlated
Tashiro et al. ⁴³	Various	11 C-, 5 C+	Cross-section	FDG-PET, SR	Cancer: Metabolism correlated with social desirability
Kumano et al. ⁴¹	Various	6 C+, 13 C-	Longitudinal	FDG-PET, SR	Cancer: BL metabolism associated with depression change over time
Golan et al. ⁴⁷	lung	18 PC, 8CS, 11 L	PC cross-section	FDG-PET	PC: metabolism
Benveniste et al. ⁴⁸	lung	17 PC, 15 H	PC cross-section	1H-MRS	PC: Neural markers

PC=cancer patients who have not yet received chemotherapy, C+=cancer patients treated with chemotherapy, C-=cancer patients not treated with chemotherapy, H=healthy controls, CS=cancer survivors, L=individuals with benign lesions, FDG-PET=[F-18] Fluorodeoxyglucose positron emission tomography, SR=self-reported cognitive/psychological measures, NKA = natural killer cell activity, =decrease, =increase, BL = baseline, Cancer=individuals with cancer, regardless of treatment status or time