A systemic literature review of neuroimaging studies in women with breast cancer treated with adjuvant chemotherapy

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Chemotherapy-induced cognitive deficits in patients with breast cancer, predominantly in attention and verbal memory, have been observed in numerous studies. These neuropsychological findings are corroborated by the results of neuroimaging studies. The aim of this paper was to survey the reports on cerebral structural and functional alterations in women with breast cancer treated with chemotherapy (CTx). First, we discuss the host-related and disease-related mechanisms underlying cognitive impairment after CTx. We point out the direct and indirect neurotoxic effect of cytostatics, which may cause: a damage to neurons or glial cells, changes in neurotransmitter levels, deregulation of the immune system and/or cytokine release. Second, we focus on the results of neuroimaging studies on brain structure and function that revealed decreased: density of grey matter, integrity of white matter and volume of multiple brain regions, as well as their lower activation during cognitive task performance. Finally, we concentrate on compensatory mechanisms, which activate additional brain areas or neural connection to reach the premorbid cognitive efficiency.

Key words: neuroimaging, cognition, breast cancer, chemotherapy.

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Introduction

The results of neuropsychological examinations carried out over the last two decades indicate the occurrence of cognitive impairments in patients with breast cancer who received chemotherapy [1]. A recent metaanalysis [2] showed a decrease in capacity of attention and selective attention as well as in immediate and delayed verbal recall in patients treated with chemotherapy compared to healthy persons. Changes observed during neuropsychological testing are corroborated by the results of neuroimaging studies carried out in the recent years [3–18].

The aim of this paper is to analyse the results of the neuroimaging studies conducted to date, assessing the cerebral alterations of women with breast cancer treated with chemotherapy.

The paper first focuses on the mechanisms underlying the cognitive decline, then describes the results of the studies on the structural and functional changes in the brain, and finally reports on the compensatory mechanisms observed in chemotherapy-treated women with breast cancer.

Mechanisms of chemotherapy-induced cognitive impairments

The mechanisms of cognitive impairment after chemotherapy (CTx) are still not fully understood [19, 20]. The potential role of various factors is indicated, related both to individual characteristics (host-related, soil characteristics) and the neoplastic disease itself (disease-related, seed characteristics) [21].

Research results imply a direct neurotoxic effect of cytostatic agents, which cross the blood-brain barrier causing, for exzample damage to neurons or glial cells, changes in neurotransmitter levels [22–26], and microvascular damage related to ischemia and brain damage, such as decreased vascular density in the hippocampus after the use of methotrexate [19, 27]. The indirect mechanisms are associated with the deregulation of the immune system and/or release cytokines [22, 28, 29], hormonal changes, e.g., decreased levels of oestrogen and progesterone due to premature menopause [30, 31], or DNA damage due to the effect of oxidative stress and accelerated telomere shortening [22, 28]. Moreover, the significance of individual factors associated with age, vascular risk factors, or the pre-cancer level of cognitive functioning and the amount of cognitive reserves, is also pointed out [31].

The results of more recent studies indicate that some patients may exhibit genetic predisposition to cognitive impairments [20, 31]. A relationship has been shown between the allele ε4 of apolipoprotein E (APOE) gene and the deterioration of cognitive functioning in patients previously treated for

breast cancer or lymphoma [26]. It was also found that persons with the catechol-O-methyltransferase (COMT)-Val genotype are more susceptible to the negative effects of CTx on cognitive functioning [32]. Genetic polymorphism may be related to the effectiveness of the blood-brain barrier (e.g. different expression of the multidrug resistance gene encoding P-glycoprotein, MDR1), the functioning of cytokines (e.g. polymorphism of the interleukin 6 cytokine gene), neurotransmitters (e.g. the polymorphism of COMT gene), and DNA repair mechanisms (e.g. the polymorphism of the X-ray repair cross complementing protein gene, XRCC1) [22, 33].

Methods

A comprehensive literature search was conducted using the PubMed database. The following search terms and their derivatives were used: cognition, neuroimaging, fMRI, PET, MRI, chemotherapy, breast cancer. Studies had to assess brain functioning with neuroimaging methods, be published in a peer-reviewed journal, and be available as full text in English language. No time period was specified.

Results

Forty-one studies fulfilled the inclusion criteria and were selected for further analysis. Changes in the central nervous system of women with breast cancer (BC) treated with CTx were assessed in 15 studies using an MRI [6, 10–13, 34–43] and in 24 studies using functional neuroimaging methods [3, 5, 7–9, 14–18, 44–57]. In two studies both structural and functional changes were assessed [4, 58]. The characteristics of structural and functional studies in breast cancer patients are presented in Tables 1–4.

Structural changes in the central nervous system of women with breast cancer treated with chemotherapy

In ten studies researchers used Voxel-Based Morphometry (VBM) [4, 6, 12, 37–42, 58] to compare the volume of brain areas and the density of grey and white matter [59]. In five studies Diffusion-Tensor Imaging (DTI) [11, 35, 36, 38, 43] was used to measure the microstructural integrity of white matter using fractional anisotropy (FA) and structural connectivity of the brain [60] was applied. In

Table 1. Structural cerebral changes in breast cancer patients prior and after chemotherapy

Assessment	Grey matter changes	White matter changes
Prior to CTx	↔ hippocampal volume in BC CTx+ and CTx– [34] ↔ density and volume of GM between BC CTx+/CTx–/HC [37, 41, 58] ↔ GM volume in DLPFC and superior parietal cortex between BC CTx+/CTx–/HC [58] ↓ left cingulate GM density in BC CTx– compared to HC [12]	↓ WM volume in frontal, parietal and limbic regions depending on type of analyses and covariates entered [41] ↓ WM integrity in BC compared to HC [58]
1–12 months after CTx	↓ prefrontal, parahippocampal, cingulate gyrus, precuneus volume [6] ↓ bilateral frontal, temporal (including hippocampus and adjacent medial temporal structures) and cerebellar regions and right thalamus GM density in BC CTx+ than HC [37] ↓ left frontal CH density in BC CTx+ compared to HC [12] ↓ frontal, temporal, parietal, and occipital volume [42]	↓ FA in frontal, parietal and occipital tracts after CTx+ [11, 36] ↓ prefrontal, parahippocampal, cingulate gyrus, precuneus volume [6]
1–2 years after CTx	↓↑ bilateral superior frontal, left middle frontal, right superior temporal and cerebellar GM density [37] ↓ persisted in bilateral cerebellum, right thalamus and medial temporal lobe, left middle gyrus and right precentral, medial frontal and superior frontal gyri [37] ↓ in bilateral frontal and temporal regions [42] ↓ global hippocampal volume in 8% of BCS CTx+ [10] ↓ posterior hippocampus in 11% BCS CTx+ compared to HC [10]	↓ FA in genu of corpus callosum in BCS CTx+ than HC [35]
2–10 years after CTx	↔ prefrontal, parahippocampal, cingulate gyrus, precuneus volume between BCS CTx+/CTx–/HC [6] ↓ posterior cortical regions and cerebellum volume in BCS HCTx+ compared to CTx– [38] ↓ small-world characteristics of GM; altered interactions in frontotemporal regions; fewer network hubs in BCS CTx+ compared to HC [40] ↓ left hippocampal volumes in BCS CTx+ compared to HC [13]	↓ white matter integrity BCS HCTx+ compared to CTx– [38]
> 10 years after CTx	↓ total brain and GM volume in BSC CTx+ compared to reference group [39]	↔ prevalence of infractions or WM lesions volume in BSC CTx+ than reference group [43] ↑ prevalence of total cerebral microbleeds (CMBs) and CMBs in deep/infratentorial regions in BSC CTx+ than reference group [43]

↔ no changes/no differences; ↓ decrease/smaller; ↑ increase/higher; ↓↑ recovery
CTx+ – cancer patients treated with standard dose of chemotherapy; HCTx+ – cancer patients treated with high-dose chemotherapy; CTx– – cancer patients without chemotherapy; BC – breast cancer patients; BCS – breast cancer survivors; HC – healthy controls; FA – fractional anisotropy; GM – grey matter; WM – white matter

one study semi-automatic segmentation procedure was used [34] and in three automatic seqmentation procedure were used [10, 13, 39]. Most of the studies were conducted in cross-sectional design: 10 in breast cancer survivors treated with CTx [4, 6, 10, 13, 34, 35, 38–40, 43] and 2 in breast cancer patients prior to CTx [41, 58]; 5 studies were conducted with longitudinal design [11, 36, 37, 61, 62]. The results obtained from breast cancer patients treated with CTx were compared to breast cancer patient without CTx [34, 38, 55], healthy controls [4, 10, 13, 35, 40, 41, 62], non-cancer reference subjects [39, 43], or breast cancer patients without CTx and healthy controls [6, 36, 37, 58, 61]. In four studies breast cancer patients were treated with the same schema of CTx [38, 39, 43, 58] and in the other studies different schemas were applied [4, 6, 10–13, 34–37, 40, 42]. A summary of the structural cerebral changes described in analyzed studies is presented in Table 1.

The evaluation of the anatomical properties of the brain using MRI yields information on the structural changes occurring over time and makes it possible to discern the differences between groups. As already mentioned in the discussion of some of the studies, supplementing the research using MRI with functional imaging techniques is a method to obtain fuller descriptions of chemotherapy-related cognitive impairment (CRCI) [63].

Functional changes in the central nervous system of women with breast cancer treated with chemotherapy

The functional studies were carried out using fMRI [4, 5, 7, 8, 14–16, 18, 48–55, 57, 58, 64], EEG [44, 45, 65], resting state fMRI [3, 17], PET [9] and Pulsed Arterial Spin Labelling MRI Perfusion [56]. During fMRI cognitive processes were assessed using verbal and visual working memo-

Table 2. Functional changes in breast cancer patients prior to and after chemotherapy

Assessment	Functional changes
Prior to CTx	↑ bifrontal and biparietal regions in high load task in BC compared to HC [48] ↑ inferior frontal gyrus, insula, thalamus and midbrain during working memory in BC [49] ↑ bifrontal and ↓ left parietal in BC CTx+/CTx– compared to HC [8] ↓ cerebellar in BC than NCN [50] ↑ prefrontal with increasing task difficulty on a planning task compared to HC, but not during a memory task [58] ≠ neural response – ↑ spatial variance in executive network activity [54] ↔ in the multitasking network [55] ↔ perfusion in GM between BC CTx+/CTx– [56]
1–12 months after CTx	↓ in bifrontal regions in BC CTx+/CTx– [8] ↓ in left inferior frontal when comparing to prior CTx+ [8] ↑ in left thalamic and posterior middle temporal gyrus compared with HC and ↑ in right cerebellar and left inferior precentral and posterior middle temporal gyrus compared with the CTx– [8] ↓ bilateral insula, left inferior orbitofrontal cortex and left middle temporal gyrus [15] ↑ brain activity magnitude in BC CTx+ with CIA [52] ↓ functional connectivity [53] ↓ in the multitasking network [55] ↓ in frontospatial executive network and cognitive complaints [18] ↑ perfusion in superior and posterior regions in BC CTx+ not related with ↓ frontal GM density, however ↓ frontal GM density was associate with ↓ perfusion in bilateral frontal and parietal lobes [56] ≠ resting state functional connectivity in BCS women with subjective cognitive complaints [17]
1–2 years after CTx	↑ in bifrontal and biparietal regions during cognitive task but not significant differences in test performance [46] ↓↑ in left frontal region as prior to CTx; ↓ persisted in middle frontal gyrus [8] ↑ partial return to baseline in the dorsal attention network [53]
2–10 years after CTx	↓ earlier P3 component in BCS CTx+ [44, 65] ↓ amplitude of P3 component in BCS H CTx+ [45, 65] ≠ cerebral blood flow in frontal cortex and cerebellum during memory task in BCS CTx+ [9] ↓ left middle dorsolateral prefrontal cortex and premotor cortex in BCS CTx+ compared to HC, ↓ left caudal prefrontal cortex and worse test performance in BCS CTx+ compared to CTx– and HC [7] ↓ prefrontal and parietal areas in BCS CTx+ compared to CTx–; ↑ frontal activation – better test performance [5] ≠ global brain network organisation: ↑ global clustering, ≠ regional network characteristics in frontal, striatal and temporal areas [3] ↓ left precuneus connectivity in AC CTx+ and ↓ verbal performance [16] ≠ default mode network resting-state functional connectivity [51] ↓ prefrontal cortex during encoding task [14] ↑ in right superior temporal gyrus extending into bilateral fusiform, bilateral lingual gyri, left hippocampus, bilateral basal ganglia, right precentral gyrus, right superior and inferior frontal gyri, right middle frontal gyrus, bilateral inferior frontal gyrus, right cingulate gyrus, bilateral insula, bilateral parahippocampal gyrus, bilateral cuneus, bilateral precuneus, bilateral superior parietal lobe, and cerebellum during recall task [14]
> 10 years after CTx	↓ prefrontal and parietal areas [57]

↔ no changes/no differences in activation; ↓ decreased activation; ↑ increased activation; ≠ altered activation;
↓↑ recovery CTx+ cancer patients treated with standard dose of chemotherapy; HCTx+ – cancer patients treated with high-dose chemotherapy; CTx– – cancer patients without chemotherapy; BC – breast cancer patients; BCS – breast cancer survivors; HC – healthy controls; NCN – non-cancer controls; CIA – chemotherapy-induced amenorrhoea

Table 3. Characteristics of structural studies in breast cancer patients

Study	Population	Major CTx treatment	Design	Neuroimaging method	Major findings
Yoshikawa *et al.* 2005 [34]	44 BCS CTx+ A: 48.3 ±5.7; 31 BCS CTx– A:48.2 ±5.7;	CMF 32%; AC 30%; 5FU 21%;	CS; TSCTx 1262 ±396 days	MRI; ASP	No differences in hippocampal volume
Inagaki *et al.* 2007 [6]	S1: 51 BCS CTx+ A: 47.3 ±5.2; 54 CTx– A: 46.3 ±6.1; 55 HC A: 46.2 ±6.7 S2: 73 BCS CTx+ A: 48.2 ±5.6; 59 BSC CTx– A: 48.4 ±4.8; 37 HC A: 48.0 ±6.4	S1: CMS 78%; AC: 6%; UFT: 10%; S2: CMF: 51%; AC: 20%; UFT: 10%	CS: S1 < 1 year; TSCTx 119 days ±47 S2 ± 3 years; TSCTx 1189 days ±359	MRI; VBM	1 year after treatment smaller GM WM in prefrontal, parahippocampal, cingulate gyrus and precuneus; these regions correlated with indices of attention/concentration and/or visual memory; 3 years after no differences in GM and WM between CTx+, CTx– and HC
Abraham *et al.* 2008 [35]	10 BCS CT+ A:49.8 ±8.0 9 HC A: 46.8 ±6.8	AC: 50%; AC-T: 50%	CS; TSCTx: 22 ±10 months	MRI; DTI	Lower FA in the genu of the corpus callosum in BCS than HC. Positive correlation between FA in the genu and processing speed
Deprez *et al.* 2010 [36]	34 BC CTx+ A: 43.7 ±6.1; 16 BC CTx– A: 43.1 ±5.7; 19 HC A: 43.8 ±4.9	UNK	L; T1: before CTx; T2: 3–4 months after CTx	MRI; DTI	Decreased FA in frontal, parietal and occipital WM tracts in CTx+ in T2 compared to T1. No changes in CTx– and HC
McDonald *et al.* 2010 [37]	17 BC CTx+ A: 52.4 ±8.5; 12 BC CTx– A:52.7 ±7.2; 18 HC A: 50.6 ±6.5	AC-T: 71%; AC: 18; TAC 11%	L; BC CT+: T1: before CTx; T2: 1 month after CTx; T3: 1 year after CTx; BC CTx–/HC yoked intervals	MRI; VBM	Pre-chemotherapy no between-group differences in GM 1 month after CTx reduced bilateral frontal, temporal, and cerebella GM density in BC relative to HC 1 year after CTx changes improved in some regions and persisted with others CTx– reduced right cerebellar GM density relative to HC in T2
Bergouignan *et al.* 2011 [10]	16 BCS CTx+ A: 48.7 ±5.0; 21 HC A: 47.7 ±5.3	UNK	CS; TSCT > 18 months	MRI; ASP	The global hippocampal volume reduces in 8% and posteriori hippocampus in 11% in BC compared to HC. Reduced autobiographical memory related to posteriori hippocampal volume
Deprez *et al.* 2012 [11]	34 BC CTx+ A: 43.7 ±6.1; 16 BC CTx– A: 43.1 ±5.7; 18 HC A:43.8 ±4.9	FEC: 35%; FEC-T: 65%	L; T1: before CTx; T2: 3–4 months after CTx; CTx–/HC yoked intervals	MRI; DTI	Decrease of FS in frontal, parietal, and occipital WM tracts after CTx compared baseline. Mean regional FA changes correlated with attention and verbal memory in BC CTx+ group
de Ruiter *et al.* 2012 [38]	17 BCS CTx+ A: 56.5 ±5.1; 15 BCS CTx– A: 58.2 ±5.8	FEC+ CTC + autologous peripheral blood hematopoietic progenitor-cell transplantation rescue 100%	CS; TSCTx 9.5 ±0.8 years	MRI; DTI; VBM	Reduced GM volume in posteriori cortical regions and cerebellum in CTx+ BCS compared to CTx–. GM reduction in left posterior parietal cortex overlapped with fMRI hypoactivation during memory encoding and colocalised with WM abnormalities. Reduced WM integrity in CTx+
Hosseini *et al.* 2012 [40]	37 BCS CTx+ A: 54.2 ±6.1; 38 HC A: 55.5 ±9.0	AC-T: 43%; AC: 24%; CT: 16%	CS; TSCTx: 4.5 ±3.4 years	MRI; VBM; Graph theoretical analysis of GM structural networks	Reduced small-world characteristics of GM, altered interactions in frontotemporal regions and fewer networks hubs in BC compared to HC
Koppelmans *et al.* 2012 [39]	184 BCS CTx+ A: 64.0 ±6.5; 368 non-cancer reference subjects A:64.0 ±6.5	CMF 100%	CS; TSCTx: 21.1 ±4.4 years	MRI; VBM; ASP	Smaller total brain and GM volume in BC compared to reference subjects. Observed smaller GM volume comparable to the effect of almost 4 years of aging
Scherling *et al.* 2012 [41]	23 BC CTx+ A: 51.0 ±8.5; 23 HC A: 50.0 ±9.0	NA	CS; BC prior to CTx	MRI; VBM	No differences in GM between BC and HC. Lower WM volumes in frontal, parietal and limbic regions in BC than in HC. Findings modified by inclusion of covariates
Conroy *et al.* 2013 [4]	24 BCS CTx+ A: 57.8 ±9.6; 23 HC A: 61.2 ±9.9	AC: 29%; AC-T: 21%; A-T: 12%	CS; TSCTx 6.4 ±2.1 years	MRI; VBM	Decreased GM density in several brain regions in BC compared to HC. GM density negatively related to oxidative DNA damage and learning and memory performance. Post CTx interval positively related to right frontal GM density (related to cognition)

Table 3. Cont.

Study	Population	Major CTx treatment	Design	Neuroimaging method	Major findings
Kesler *et al.* 2013 [13]	42 BC CTx+ A: 54.6 ±6.5; 35 HC A: 55.5 ±9.3	AC or CT: 86%; 5FU-T or M: 14%	CS; TSCTx 4.8 ±3.4 years	MRI; automated hippocampal segmentation	Reduced left hippocampal volumes and elevated interleukin-6 and tumour necrosis factor α in BC compared to HC. Cytokine levels and left hippocampal volume in both groups associated with verbal memory performance
McDonald *et al.* 2013 [12]	27 BCS CTx+ A: 49.9 ±7.6; 28 BCS CTx– A: 52.4 ±9.1; 24 HC A: 47.0 ±9.2	AC-T 33%; CT 33%; D/ carboplatin 18%	L; T1: before CTx; T2: 1 month after CTx; BC CTx–/ HC yoked intervals	MRI; VBM	Pre-chemotherapy reduced left cingulate GM density in BCS CTx– compared to HC. 1 month after CTx reduced left frontal GM density in BCS CTx+ compared to HC. Left frontal GM density related to self-reported executive function
Lepage *et al.* 2014 [42]	19 BC CTx+ A 50.2 ±8.6; 19 HC A: 49.3 ±9.0	FEC-D: 68%;	L; T1: before CTx; T2: 1 month after CTx; T3: 1 year after CTx	MRI; VBM	In BC group distributed GM volume reductions 1 month after CTx, a partial recovery 1 year after CTx with persisted alterations in frontal and temporal regions
Koppelmans *et al.* 2015 [43]	187 BCS CTx+ A: 64.1 ±6.5; 374 non-cancer reference subject A: 64.1 ±6.5	CMF: 100%	CS; TSCTx 21.1 4.3 years	MRI; DTI	Higher prevalence of total cerebral microbleeds and in deep/infratentorial region in BSC than in reference group. No differences in the prevalence of infractions or WM lesion volume
Menning *et al.* 2015 [58]	32 BC CTx+ A: 50.2 ±9.2; 33 BC CTx– A: 52.4 ±7.3; 38 HC A: 50.1 ±8.7	anthracycline	CS; before CTx	MRI; VBM	Lower WM integrity in BC compared to HC. Alterations associated with symptoms of fatigue. No differences in regional GM and WM volumes. No differences in GM volume of ROIs in the DLPFC and superior parietal cortex between groups

CTx+ – cancer patients treated with standard dose of chemotherapy; HCTx+ – cancer patients treated with high-dose chemotherapy; CTx– – cancer patients without chemotherapy; BC – breast cancer patients; BCS – breast cancer survivors; HC – healthy controls; SRCI – self-reported cognitive impairment; A – mean ± SD age; TSCTx – mean ± SD age time since chemotherapy; DTI – diffusion tensor imaging; MRI – magnetic resonance imaging; FA – fractional anisotropy; VBM voxel based morphometry; ASP – automatic segmentation procedure; ROI – region of interes; GR – gray matter; WM – white matter; CS – cross-sectional; L – longitudinal; T – time point; S – sample

Adjuvant chemotherapy: CMF – cyclophosphamide, methotrexate, fluorouracil; AC – cyclophosphamide, doxorubicin; CAF – fluorouracil, cyclophosphamide, doxorubicin; 5FU – fluorouracil; UFT – tegafur, uracil; AC-T – AC followed by a taxane; TAC – docetaxel, doxorubicin, cyclophosphamide; A-T – doxorubicin, taxane; CT – cyclophosphamide, paclitaxel; CD – cyclophosphamide, docetaxel; D – docetaxel; M methotrexate; UNK – not known; NA – not applicable

ry tasks [4, 8, 18, 46, 48, 49, 52–54], visual memory task [5, 57], verbal memory task [9, 14–16], attention [53] and executive functioning [5, 7, 41, 55, 57]. Most studies were conducted in cross-sectional design: 14 in breast cancer survivors treated with CTx [3–5, 7, 9, 14, 16, 17, 44–46, 51, 57, 65] and 4 in breast cancer patient prior to CTx [48–50, 58]; 8 studies were conducted in longitudinal design [8, 15, 18, 52–56]. The results obtained by breast cancer patients treated with CTx were compared with breast cancer patients without CTx [7, 8, 16, 18, 38, 44, 45, 54–56], with breast cancer patients treated with different schemas of CTx [9, 16, 45, 57, 65], with patients treated with radiotherapy [57], with healthy controls [3, 4, 8, 14, 15, 18, 46, 48, 52, 57], or non-cancer reference subjects [49, 50] or with breast cancer patients without CTx and healthy controls [7–9, 18, 51, 54–56]. In three studies breast cancer patients were treated with the same schema of CTx [44, 45, 65], and in the others studies different schemas were applied [3, 4, 7, 8, 14–18, 45–48, 50–57].

Summary of functional changes described in the analysed studies (Table 2).

Compensatory mechanisms

An interesting study to observe the mechanism underlying the process of coping with cognitive demand was performed on 60-year-old homozygous twin sisters [46]. One of the sisters was previously (22 months earlier) treated for breast cancer that AC+T adjuvant chemotherapy (four cycles of AC followed by four cycles of T – docetaxel), and received hormonal therapy (tamoxifen) during the study. While diseases and therapies which could negatively affect cognitive functioning were excluded in both sisters, they were found to have the allele ε4 of apolipoprotein E, associated with the occurrence of cognitive deficits [26]. Cognitive functioning was evaluated using standard neuropsychological tests, a self-assessment questionnaire, and functional magnetic resonance imaging (fMRI). It was found that the twin treated with CTx reported much greater problems with cognitive functioning. Nevertheless, the results of the performed neuropsychological tests lay within the norm and differed minimally from those of the healthy sister. The fMRI results showed white matter hyperintensities in both sisters, which are also observed among the carriers of the allele ε4 of apolipoprotein E [66, 67]. No coherent pattern of the differences in the volumes of selected brain areas (including the hippocampus, amygdala, frontal part of the hippocampal gyrus cortex, and corpus callosum) were found between sisters. Nonetheless, interesting results were obtained in an fMRI examination during the performance of a task evaluating working

Table 4. Characteristics of functional neuroimaging studies in breast cancer patients

Study	Population	Major CTx treatment	Design	NI/NP methods	Major findings
Kreukels *et al*. 2005 [44]	26 BCS CT+ A: 51.5 ±5.6; 23 BCS CT– A: 53.2 ±8.5	CMF: 100%	CS; TSCTx: CTx+: 5.1 years; CTx–: 3.6 years	EEG	Differences in latency and amplitude of P3 component between BCS CTx+ and CTx–. Earlier and reduced P3 in CTx+
Kreukels *et al*. 2006 [45]	12 BCS HCTx+ A: 51.5 ±5.6; 17 BCS CTx+ A: 51.2 ±5.9; 23 BCS CTx– A: 53.2 ±8.5	HCTx+: FEC-CTC with autologous peripheral blood hematopoietic progenitor cell transplantation; CTx+: FEC 100%	CS; TSCTx: HCTx+: 3.7 ±0.8 years; CTx+: 4.1 ±0.7 years	EEG	Reduced amplitude of the P3 component in BCS treated with with high dose chemotherapy compared with BCS without CTx
Ferguson *et al*. 2007 [46]	2 monozygotic twins A: 60 years; Twin A: BC CTx+ Twin B: HC	AC-D	CS; TSCTx: 22 months	fMRI; verbal N-back task	Broader spatial extent of activation in typical memory circuitry (bifrontal and biparietal regions), more cognitive complaints in BC twin. Small differences in neuropsychological test performance
Silverman *et al*. 2007 [9]	5 BCS CTx+ A: 47.6 ±6.0; 11 BCS CTx+ TAM A: 51.7 ±4.7; 5 BCS CTx– A:53.2 ±4.1; 3 HC A: 57.9 ±7.1	UNK	CS; TSCTx: 5–10 years	PET; verbal memory task	Altered cerebral blood flow in frontal cortex and cerebellum during memory task in BCS CTx+. Altered cerebral activation in inferior frontal gyrus in CTx+. Correlation between resting metabolism and task performance
Kreukels *et al*. 2008 [65]	17 BCS FEC CTx+ A: 51.2 ±5.9; 12 BSC CTC CTx+ A: 51.5 ±5.6; 24 BCS CMF CTx+ A: 51.4 ±5.7; 23 BCs CTx- A: 53.2 ±8.5	FEC: 100%; FEC/CTC: 100% CMF: 100%	CS; TSCTx: 3–6 y	EEG	Lower P3 amplitudes in BCS CTx+ than in BCS CTx-. Differences in P3 latency between BCS treated with different CTx+ regimes
Kesler *et al*. 2009 [14]	14 BCS CTx+ A: 55.1 ±8.0; 18 HC A: 54.2 ±8.0	CMF: 36% AC-T: 64%	CS; TSCTx: 3.3 ±3.3 years	fMRI; verbal declarative memory task	Reduced activation in prefrontal cortex during encoding task and increased activation in multiple diffuse brain regions during recall task in BC compared to HC
Cimprich *et al*. 2010 [48]	10 BC CTx+ A: 45 ±8 9 HC A: 52 ±10	NA	CS; before CTx	fMRI; verbal working memory test	Increased bifrontal and biparietal activation at high task load in BC before CTx compared to HC
Kesler *et al*. 2011 [7]	25 BC CTx+ A: 56.2 ±7.8; 19 BC CTx– A: 58.1 ±6.5; 18 HC A: 55.6 ±9.4	CTA or CA: 36%; AC: 28%; CMF: 12%	CS; TSCTx: 4.7 ±5.9 years	fMRI; Wisconsin card sorting	Reduced activation in the left middle dorsolateral prefrontal cortex and premotor cortex in BC compared to HC. Reduced left caudal lateral prefrontal cortex activation and increased perseverative errors and reduced processing speed in BC CTx+ compared to BC CTx– and HC
de Ruiter *et al*. 2011 [5]	19 BCS CTx+ A 56.3 ±5.5; 15 BCS CTx– 58.2 ±5.8	FEC-CTC with autologous peripheral blood hematopoietic progenitor cell transplantation: 100%	CS; TSXTx: 9.8 ±0.8 years	fMRI; Tower of London; Paired associates task	Reduced prefrontal and parietal activation in BC CTx+ compared to BCS CTx–. In BC CTx+ greater frontal activation related to better performance in Tower of London task
Scherling *et al*. 2011 [49]	23 BC A: 51.5 ±8.47; 23 NCN A: 50.4 ±8.82	NA	CS; before CTx	fMRI; visuospatial n-back task	Increased activity in inferior frontal gyrus, insula, thalamus and midbrain during working memory in BC compared to NCN. Findings modified by inclusion of covariates
Bruno *et al*. 2012 [3]	34 BCS CTx+ A: 55.16 ±7.3; 27 HC A: 55.08 ±9.12	ACT: 79%; CMF: 15; AC + CMF: 9%	CS; TSXTx: 5.35 ±5.40 years	Resting state fMRI	Alteration in functional brain networks supporting executive functioning, memory and emotion regulation in BC CTx+ compared to HC. No correlation between functional brain network, objective and subjective cognitive measures

Table 4. Cont.

Study	Population	Major CTx treatment	Design	NI/NP methods	Major findings
McDonald *et al*. 2012 [8]	16 BC CTx+ A: 52.9 ±8.6; 12 CTx– A: 52.7 ±7.2; 15 HC A: 50.5 ±6.0	ACT: 69%; TAC: 12%; AC: 19%	L; T1: before CTx; T2: 1 month after CTx; T3: 1 year after CTx	fMRI; verbal N-back task	In both BC groups increased activation in bifrontal in T1, reduced activation at T2; in some regions return to baseline at T3 – suggesting compensatory recruitment during working memory task. In BC CTx+ decreased left frontal activation in T2 comparing to T1 but returning to baseline at T3 – possible effect of CTx
Scherling *et al*. 2012 [50]	23 BC A: 51.5 ±8.47; 23 NCN A: 50.4 ±8.82	NA	CS; before CTx	fMRI; go/no-go task	In BC less activity in cerebellar area than in NCN
Kesler *et al*. 2013 [51]	30 BCS CTx+ A: 55 ±7; 27 BCS CTx- A: 58 ±7; 24 HC A: 56 ±9	AC-T: 87%	CS; TSCTx 4.5 ±3.3 years	fMRI	Default mode network resting state functional connectivity patterns disturbed in BCS CTx+ t
López Zunini *et al*. 2013 [15]	21 BC A: 50.62 ±8.37; 21 HC A: 49.67 ±8.75	FECT: 62%; CD: 19% AC: 19%	L; T1: before CTx; T2: 1 m after CTx	fMRI; verbal memory recall	In BC decrease activation in the bilateral insula, the left inferior orbitofrontal cortex and the left middle temporal gyrus post-chemotherapy in compared to pre-chemotherapy, and to HC
Conroy *et al*. 2013 [4]	24 BSC CTx+ A: 57.8 ±9.6; 23 HC A: 61.2 ±9.9	AC: 29%;	AC-T: 21%; A-T: 12%	CS; TSCTx: 6.4 2.1 years	fMRI; visual n-back Lower activation in several regions in BCS. Activation in the right anterior frontal region positively correlated with post-chemotherapy interval
Conroy *et al*. 2013 [52]	9 BC CTx+ with CIA A: 45.3 ±5.8; 6 BC CTx+ post-menopausal A: 58.7 ±4.4; 6 HC pre-menopausal A: 44.8 ±4.0; 6 HC post-menopausal A: 55.2 ±4.0	AC-T: 78%; AC: 11%	L; T1: before CTx; T2: 1 month after	fMRI; visual n-back	Increase in magnitude of brain activity from T1 to T2 only in BC with CIA. Changes in brain activity correlated with changes in processing speed. Pattern of change in brain activity before and after CTx varies according to pre-treatment menopausal status
Dumas *et al*. 2013 [53]	9 BCS CTx+ A: 57.10 ±8.6;	C: 100%; T: 89%; A: 44%	L: T1: before CTx+; T2: 1 month after; T3: 1 year after CTx+	fMRI; n-back task	Decreased functional connectivity 1 month after CTx+, partially returned to baseline in the dorsal attention network 1 year after CTx+. Decreased connectivity in the default mode network at T1 an T2. Increase in subjective memory complaints one month and 1 year after CTx
Askren *et al*. 2014 [54]	28 BSC CTx+A: 50 ±10; 37 BCS CTx– A: 53 ±9; 32 HC A: 50 ±9	AC-P: 79%; C-D: 18%; AC: 3%	L:, T1: before CTx; T2: 1–5 months after CTx	fMRI; verbal working memory task	Greater pre-treatment fatigue in CTx+ than in HC and compromised neural response characterized by higher spatial variance in executive network activity in CTx+ than in CTx-. Pre-treatment neural inefficiency in executive network was a better predictor of postchemotherapy cognitive and fatigue complaintes than chemotherapy per se
Deprez *et al*. 2014 [55]	18 BC CTx+ A: 43.7 ±4.3; 16 BC CTx- A: 44.3 ±4.7; 17 HC A: 40.7 ±6.0	FEC-T: 94%; FEC: 6%	L; T1: before CTx+; T2: 4–6 months after CTx;	fMRI; multitask paradigm	Decreased activation in the multitasking network in T2 compared to T1 in BCS CTx+. No differences between groups at T1. In BCS CTx+ increase of cognitive complaints in T2
Nudelman *et al*. 2014 [56]	27 BC CTx+ A: 49.9 ±7.6; 26 BC CTx– A: 52.0 ±8.9; 26 HC A: 48.4 ±10.1	AC-P: 30%; AC: 30%; A+carboplatine: 22%	L; T1: after surgery before other treatments; T2: 1 month after CTx or yoked intervals	pulsed arterial spin labeling MRI; VBM	No differences in baseline perfusion between groups. Increased perfusion 1 month after CTx compared to baseline in right precentral gyrus

Table 4. Cont.

Study	Population	Major CTx treatment	Design	NI/NP methods	Major findings
Kesler *et al.* 2015 [16]	20 BCS ACTx+ A: 52 ±7.6; 19 BCS CTx+ A: 53 ±8.7; 23 BC CTx– A: 58 ±7.9	ACTx+: AC-P: 74%; AC: 10%; CAF 5%; CTx–: CP: 79%; CMF: 11%	CS; TSCTx: CTx+AC: 2.2 ±1.5 years; TSCTx: CTx+: 2.1 ±1.6 years	fMRI; The Hopkins Verbal Learning Test–Revised	Lower verbal memory performance (immediate and delayed recall), lower left precuneus connectivity in BC treated with anthracycline-based CTx compared to BC treated with non-anthracycline regiments and HC
Menning *et al.* 2015 [58]	32 BC CTx+ A: 50.2 ±9.2; 33 BC CTx- A: 52.4 ±7.3; 38 HC A: 50.1 ±8.7	antracycline	CS; before CTx	fMRI; Tower of London; Paired Associates paradigm	Hyperactivation in prefrontal area with increasing task difficulty on a planning task in both BC groups compared to HC, but not during a memory task. Observed changes were associated with symptoms of fatigue
Piccirillo *et al.* 2015 [17]	15 BCS CTx+ with SRCI A: 54; 13 BC CTx+ without SRCI A: 52	anthracyline and/or tacane	CS; TSCTx > 30 days	rs-fcMRI	Disrupted resting state functional connectivity only in BCS women who self-reported cognitive impairment
Stouten-Kemperman *et al.* 2015 [57]	17 BCS HCTx+ A: 56.3 ±5.5; 15 BCS CTx+ A: 59.8 ±6.3; 15 BCS RT A: 58.2 ±5.8; 27 HC A: 60.31 ±4.8	FEC: 100% or FEC-CTC: 100%	CS; TSCTx: 11,5 years post CTx	fMRI; Tower of London; Paired Associates paradigm	Hypoactivation in task-related prefrontal and parietal areas in both CTx+ groups compared to RT group. In HCTx+ hypoactivation more pronounced as well as worse task performance than in CTx+
Jung *et al.* 2016 [18]	28 BCS CTx+ A: 49.68 ±9.74; 34 BCS CTx– A: 53.94 ±8.42; 30 HC A: 51.13 ±8.47	AC-T: 79%; DC: 18%; AC: 4%	L: T1: before CTx+; T2: 1 month after CTx; T3: 7 months after CTx	fMRI; Verbal Working Memory Task	Changes in frontoparietal executive network, cognitive complaints at T3. Higher spatial variance (neural inefficiency) in executive network in CTx+ than in CT– and HC

NI – neuroimaging; NP – neuropsychological; CTx+ – cancer patients treated with chemotherapy; CTx– – cancer patients without chemotherapy; BC – breast cancer patients; BCS –breast cancer survivors; RT – radiotherapy; HC – healthy controls; NCN – non caner controls; TAM – tamoxifen; CIA – chemotherapy-induced amenorrhea; SRCI – self-reported cognitive impairment; A – mean SD age; TSCTx – mean SD age time since chemotherapy; DTI – diffusion tensor imaging; MRI – magnetic resonance imaging; FA – fractional anisotropy; VBM – voxel based morphometry; TIC – total intracranial volume; fMRI – functional MRI; PET – positron emission tomography; rs-fcMRI – resting-state functional-connectivity MRI; GR – gray matter; WM – white matter; CS – cross-sectional; L – longitudinal; T – time point; S – sample; adjuvant chemotherapy: CMF – cyclophosphamide, methotrexate, fluorouracil; AC – cyclophosphamide, doxorubicin; CAF – fluorouracil, cyclophosphamide, doxorubicin; 5FU – fluorouracil; UFT – tegafur, uracil; AC-T – AC followed by a taxane; A-T – doxorubicin, taxane; FECT – fluororacil, epirubicin, cyclophosphamide, docetaxel; CT cyclophosphamide, paclitaxel; CD cyclophosphamide, docetaxel; M – methotrexate; CTC – cyclophosphamide, thiotepa, carboplatin; UNK – not known; NA – not applicable

memory using the n-back paradigm. It was shown that the more the task was taxing to the working memory, the greater was the scope of activation of brain areas (bilateral stimulation of frontal and parietal areas) in the sister treated with CTx compared to the healthy one. However, no significant differences in the task performance level were observed [64].

The obtained results indicate that in order to enable the adequate performance level of a task by the twin treated with CTx, it was necessary to activate a greater area of neural networks, which most likely requires greater mental effort, reflected in the greater number of complaints about cognitive functioning [64, 68]. It may be supposed that, if the task were made increasingly more taxing, at a certain level of difficulty the compensation for the deficits would be insufficient and the test results would become poorer [68]. The activation of larger areas of the brain in order to maintain the appropriate performance level in cognitive tasks was also confirmed by numerous studies on people aging normally [69–71].

The activation of compensatory mechanisms was also confirmed in a more recent longitudinal study carried out by McDonald, Conroy, Ahles, West, and Saykin [8], which assessed working memory using the n-back paradigm and brain activation using fMRI in women with breast cancer and in healthy ones. The measurements were taken three times: before chemotherapy, and one month, and one year after treatment. The performance level of n-back tasks did not differ significantly between groups; however, changes in activation patterns were observed in all three measurements, both during greater and lesser working memory-loaded tasks. Moreover, greater activation of prefrontal areas was found in the examinations before and one year after the treatment.

Thanks to compensatory neuroplasticity, the cognitive functioning of people treated with chemotherapy can be maintained on an unchanged or only slightly deteriorated level compared to their premorbid abilities. The studies on the levels of brain activation carried out with fMRI revealed that additional brain areas become involved in the performance of lower difficulty tasks, allowing their performance to remain within the norm. A deterioration in

functioning becomes visible when the increasing difficulty exceeds the efficiency of compensatory mechanisms [68].

Conclusions

Based on the studies carried out using neuroimaging methods, it is possible to describe the cognitive deficits caused by adjuvant chemotherapy [72]. Specific, albeit small, structural changes and functional changes within the central nervous system are associated with the minor specific impairments of cognitive functions described in literature [72].

The changes in the activity of various cerebral regions in patients treated with chemotherapy indicate that the brain functions in an altered way, by activating new areas or creating new neural connections to reach the same cognitive efficiency. A greater expenditure of energy on mental activities can lead to increased fatigue and be associated with the deterioration in cognitive effectiveness and quality of life suffered by the patients [63]. Even though neuroimaging methods are not free from limitations, using them in CRCI studies in combination with self-descriptive and neuropsychological methods may yield a broader image of the described phenomenon [72].

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