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

Paulina Andryszak¹, Monika Wilkoś², Paweł Izdebski², Bogdan Żurawski³

¹Institute of Psychology, Kazimierz Wielki University in Bydgoszcz, Poland
²Department of Psychiatry, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland
³The Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland

**Review**

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

**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, tMRI, 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.

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]                       | WM volume in frontal, parietal and limbic regions depending on type of analyses and covariates entered [41] |
|                     | Density and volume of GM between BC CTx+/CTx−/HC [37, 41, 58]    | WM integrity in BC compared to HC [58]                    |
|                     | GM volume in DLPFC and superior parietal cortex between BC CTx+/CTx−/HC [58] | FA in frontal, parietal and occipital tracts after CTx+ [11, 36] |
| 1–12 months after CTx | Prefrontal, parahippocampal, cingulate gyrus, precuneus volume [6] | FA in frontal, parietal and occipital tracts after CTx+ [11, 36] |
|                     | Bilateral frontal, temporal (including hippocampus and adjacent temporal structures) and cerebellar regions and right thalamus GM density in BC CTx+ than HC [37] | FA in frontal, parietal and occipital tracts after CTx+ [11, 36] |
|                     | Left frontal CH density in BC CTx+ compared to HC [12]           | FA in genu of corpus callosum in BCS CTx+ than HC [35]    |
|                     | Frontal, parietal, and occipital volume [42]                     | FA in genu of corpus callosum in BCS CTx+ than HC [35]    |
| 1–2 years after CTx | Bilateral superior frontal, left middle frontal, right superior temporal and cerebellar GM density [37] | FA in frontal, parietal and occipital tracts after CTx+ [11, 36] |
|                     | Persisted in bilateral cerebellum, right thalamus and medial temporal lobe, left middle gyrus and right precentral, medial frontal and superior frontal gyri [37] | FA in frontal, parietal and occipital tracts after CTx+ [11, 36] |
|                     | In bilateral frontal and temporal regions [42]                  | FA in frontal, parietal and occipital tracts after CTx+ [11, 36] |
|                     | Global hippocampal volume in 8% of BCS CTx+ [10]                | FA in frontal, parietal and occipital tracts after CTx+ [11, 36] |
|                     | 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] | White matter integrity BCS HCTx+ compared to CTx− [38]    |
|                     | Posterior cortical regions and cerebellum volume in BCS HCTx+ compared to CTx− [38] | White matter integrity 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] | White matter integrity BCS HCTx+ compared to CTx− [38]    |
|                     | 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 infarctions 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] | 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

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
one study semi-automatic segmentation procedure was used [34] and in three automatic segmentation 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 Labeling MRI Perfusion [56]. During fMRI cognitive processes were assessed using verbal and visual working memo-

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**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 CN [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 gyrus, left hippocampus, bilateral basal ganglia, right precentral gyrus, right superior and inferior frontal gyr, 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]      | 51 BCS CTx+ A: 47.3 ±5.2; 54 CTx– A: 46.3 ±5.1; | CMS 78%; | AC: 6%; UFT: 10%; | 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 CTx+ A: 49.8 ±8.9; 9 HC A: 46.8 ±6.8; | AC: 50%; AC-T: 50%; | CS; TSCtx > 18 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%; | MRI; VBM | Pre-chemotherapy no between-group differences in GM 1 month after CTx reduced bilateral frontal, temporal, and cerebellum GM density in BC relative to HC 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; TSCtx > 18 months | MRI; ASP | The global hippocampal volume reduces in 8% and posterior hippocampus in 1% 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%; | 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%; | 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 211 ±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 ±5.3; 35 HC A: 55.5 ±9.3 | AC or CT: 86%; SFU-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 ±9.2; 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 ±6.6; 19 HC A: 49.3 ±9.0 | FEC-D: 68%; AC-T: 18% | CS; TSCTx 21.1 ±4.3 years | 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%; FEC-D 18%; 3 T1: before CTx; T2: 1 month after CTx; T3: 1 year after CTx | 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 infarctions 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; SRI = 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 interest; GR = gray matter; WM = white matter; CS = cross-sectional; L = longitudinal; T1 = time point; S = sample

Adjuvant chemotherapy: CMF = cyclophosphamide, methotrexate, fluorouracil; AC = cyclophosphamide, doxorubicin, CA/F = fluorouracil, cyclophosphamide, doxorubicin; S1FU = 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

Compensatory mechanisms

An interesting study to observe the mechanism underlying the process of coping with cognitive demand was performed on 60-year-old homozgous 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 memory 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]. 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).
| 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: 5.1 ±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 [63]    | 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; 18 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–: A: 58.2 ±5.8 | FEC-CTC with autologous peripheral blood hematopoietic progenitor cell transplantation: 100% | CS; TSSTx: 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.                                                                                         |
| Schering 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; TSSTx: 5.35 ±1.40 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.                                                   |
| Study                  | Population | Major CTx treatment | Design | NI/NP methods | Major findings                                                                                                                                                                                                 |
|-----------------------|------------|---------------------|--------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| McDonald et al. 2012  | 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 | 23 BC A: 51.5 ±8.47; 23 NCN A: 50.4 ±8.82 | fMRI; verbal N-back task | CS; before CTx | CS; TSCTx 4.5 ±3.3 years | Default mode network resting state functional connectivity patterns disturbed in BC CTx+ t                                                                                                                     |
| Kesler et al. 2013    | 30 BCS CTx+: A: 55 ±7; 27 BCS CTx–: A: 58 ±7; 24 HC A: 56 ±9 | AC-T: 87% | CS-T: 52% | AC: 19% | 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                                    |
| López Zunini et al. 2013 | 21 BC A: 50.62 ±8.37; 21 HC A: 49.67 ±8.75 | FECT: 62%; CD: 19% | AC-T: 21%; A-T: 12% | CS; TSCTx: 6.4 ±2.1 years | 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 |
| Conroy et al. 2013    | 24 BSC CTx+: A: 57.8 ±9.6; 23 HC A: 61.2 ±9.9 | AC: 29% | AC-T: 78%; AC: 11% | L; T1: before CTx; T2: 1 month after CTx | Increased 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     | 9 BCS CTx+: A: 57.10 ±8.6; 7 BCS CTx–: A: 56 ±9 | 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    | 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 complaints than chemotherapy per se |
| Deprez et al. 2014    | 18 BC CTx+: A: 43.7 ±8.3; 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  | 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% | 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 |
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 healthy individuals compared to RT group. In HCTx+ group, hypoactivation more pronounced as well as worse task performance than in CTx+. 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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Address for correspondence
Paulina Andryszak
Institute of Psychology
Kazimierz Wielki University in Bydgoszcz
Staffa 1
85-867 Bydgoszcz, Poland
E-mail: pandryszak@gmail.com

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