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Review

Chemobrain: A systematic review of structural and functional neuroimaging studies

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ABSTRACT

Nowadays, chemotherapy-induced cognitive impairment or 'chemobrain' is a well-established clinical syndrome, consisting of moderate to subtle cognitive changes across various domains, especially working memory, executive function and episodic verbal memory that persist only in a subgroup of long-term cancer survivors. In recent years, several studies using neuroimaging techniques have reported structural and functional neural changes associated with chemotherapy. This review provides an overview of the relevant advances that neuroimaging techniques have added to the understanding of the underlying mechanisms of chemotherapy-induced cognitive impairment. In summary, our review showed: (i) a pre-treatment (prior to chemotherapy) widespread decrease in white matter (WM) volume as well as an increased level of activation of the frontoparietal attentional network of cancer patients compared to controls; (ii) an early diffuse decrease of gray matter (GM) and WM volume together with a decrease of the overactivation in frontal regions in chemotherapy-treated patients compared to controls and (iii) a long-term persisting decrease in GM and WM volumes together with a predominantly frontal cortex hypoactivation in only a subgroup of chemotherapy-treated patients.

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1. Introduction

1.1. Chemotherapy

Chemotherapy refers to the drugs used to treat cancer patients. These drugs are used to prevent cancer cells from multiplying, invading or spreading to other tissues. Most traditional chemotherapeutic agents appear to concentrate their effect on cell proliferation. Because cell proliferation is a characteristic of many normal cells, these agents also have toxic effects on normal cells (Skeel and Khleuf, 2007). Although the blood–brain barrier (BBB) provides some protection from systemic treatments, it is increasingly recognized that many agents gain access to this environment, via direct or indirect mechanisms, potentially contributing to central nervous system (CNS) toxicity. Some chemotherapeutic agents, for example antimetabolits (as metotrexate or fluorouracil), platinum-based agents or nitrosureas, have been associated with CNS neurological toxicity (Meyers and Perry, 2008). Moreover, several risk factors on developing neurotoxicity associated with chemotherapy have been identified, including exposure to high-dose regimens (Shah, 2005), additive effects of concurrent radiotherapy administration (Sheline et al., 1980; Sul and DeAngelis, 2006), intraarterial administration with BBB disruption or intrathecal administration (Delattre and Posner, 1995). Thus, the type, dose and administration route of chemotherapy are all variables of substantial importance in understanding the effect of chemotherapy on cognitive functions.

1.2. Chemobrain: general considerations

'Chemobrain' is the term used to describe the alterations in cognitive functioning reflecting the CNS toxic effects of systemic chemotherapy. Chemotherapy-related cognitive dysfunction has become a growing matter of interest in the last ten years (Meyers and Perry, 2008). This is due to the increasing population of cancer survivors in recent years as a result of the relevant advances in cancer therapy. Although acute cognitive changes during chemotherapy are common (Ahles and Saykin, 2002; Ferguson and Ahles, 2003), long-term post-treatment cognitive changes seem to persist in only a subgroup (17–34%) of cancer survivors (Ahles and Saykin, 2007).

Reported chemotherapy-induced cognitive effects are generally modest, remaining within normal limits but with a clear impact on everyday functioning (Tannock et al., 2004). Nevertheless, the affected domains have been remarkably consistent, with the greatest differences noted in processing speed, executive functions, working memory and certain aspects of episodic memory (Jansen et al., 2005).

Mechanisms underlying this cognitive and neurobehavioral toxicity have not yet been clearly elucidated. Nevertheless, multiple candidate mechanisms for chemobrain have been proposed, including individual or cancer-related variables as well as chemotherapy-induced damage or hormonal changes (Ahles and Saykin, 2007). Unfortunately, data directly supporting the proposed mechanisms are limited (Savitz et al., 2006; Seigers and Fardell, 2011).

Concerning individual susceptibility, genetic variability in genes that regulate neural repair and/or plasticity, such as apolipoprotein E (E4) and brain-derived neurothropic factor (BDNF), genetic variability in genes that regulate neurotransmission, such as catechol-O-methyltransferase (COMT), or genetic variability in BBB transporters, as protein P-glycoprotein, might increase the vulnerability of an individual to chemotherapy-induced cognitive changes (Savitz et al., 2006; Hoffmeyer et al., 2000; Nathoo et al., 2003). Recent data from animal studies suggest that very small doses of chemotherapy can cause cell death and reduce cell division in brain structures crucial for cognition, even at doses that do not effectively kill tumor cells (Dietrich et al., 2006). Other individual variables such as age and pretreatment cognitive reserve[1] have been associated with post-chemotherapy cognitive decline, as evaluated using processing speed measures (Ahles et al., 2010). Common risk factors for the development of both cancer and neurodegenerative disorders have been also suggested, for example, poor deoxyribonucleic acid (DNA) repair mechanisms (Goode et al., 2002).

Cancer-related variables such as cytokine levels have been also related with cognitive function (Meyers et al., 2005; Seruga et al., 2008; Reichenberg et al., 2001). Cytokine are small proteins secreted by the immune system which have a described negative effect on the hippocampus (Maier and Watkins, 2003).

In addition, chemotherapy treatment can induce changes through DNA damage directly or through increases in oxidative stress, lead to the shortening of telomeres thereby accelerating cell aging, contribute to cytokine deregulation, inhibit hippocampal neurogenesis or reduce brain vascularization and blood flow (Von Zglinicki and Martin-Ruiz, 2005; de Visser et al., 2006; Seigers and Fardell, 2011). All these biological pathways may influence the extent and the recovery of the effect of chemotherapy on cognitive function. Furthermore, chemotherapy agents can be given alone or with other more specific therapies. For example, women with hormone receptor-positive breast cancer are treated with the combination of chemotherapy and hormonal therapy. Changes in levels of hormones, such as estrogen and testosterone associated with menopause or induced by hormonal therapy, have been associated with cognitive decline (Zec and Trivedi, 2002; Castellon et al., 2004). Indeed, chemotherapy might influence hormonal levels or even interact with hormones through a reduction of antioxidant capacity or the ability to maintain telomere length (Lee et al., 2005; Seigers and Fardell, 2011).

1.3. Neuroimaging studies

Structural and functional neuroimaging has been applied to examine the neural substrate of these cognitive changes in cancer patients. Voxel-based morphometry (VBM) and diffusion-tensor imaging (DTI) are structural neuroimaging techniques that are capable of detecting alterations in gray matter (GM) and white matter (WM) tissue, respectively. Moreover, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies are functional neuroimaging techniques that may contribute to detect differences in brain functioning even when there is no clear structural damage. Hence, neuroimaging studies provide a fine-grained examination of neural changes associated with chemotherapy that are relevant for a better understanding of the natural history of chemotherapy neurotoxic effects. There are a

[1] *Cognitive reserve* refers to innate and developed cognitive capacity which is influenced by genetic and experience dependent factors, as for example, education, occupational attainment, and lifestyle (Stern, 2002).

large number of investigations using such techniques in cancer populations. The purpose of this review was to summarize the current literature on the effects of chemotherapy-related cognitive changes with a focus on structural and functional neuroimaging studies.

2. Methods

The search strategy used to perform this review was designed following two steps. First, we searched the Pubmed, Psycinfo and ISI Web of Knowledge databases looking for review articles devoted to the effects of chemotherapy on the cognitive impairment of cancer patients using neuroimaging techniques. We used the keywords "*cancer*", "*imaging*", "*chemotherapy*", "*cognitive impairment*" and "*neuropsychological effect*", combined using a logical conjunction between all them, excluding the alternation between the last two keywords. The only inclusion criteria for these reviews was that they had to show, at least, evidence of chemotherapy-induced effects on structure (VBM and DTI) or brain function (PET and fMRI) derived from the utilization of these neuroimaging techniques. Second, we performed another search in the aforementioned databases looking for original articles where such imaging techniques were used to assess the effects of chemotherapy in cognitive functions or brain structure on cancer patients. Keywords used were the same as the preceding step. We applied some exclusion criteria based on the form of administration of chemotherapy. For example, articles where the patients received intrathecal or intraventricular chemotherapy were excluded. Similarly, we rejected articles where patients received cranial radiotherapy, alone or combined with other treatments. Finally, we excluded articles where there was a primary brain tumor diagnosis. In fact, after paper filtering, only breast cancer patients were included.

The majority of articles used only one of the different imaging techniques. For this reason, we grouped the articles depending on the imaging technique used: four studies used non-automatic volumetric analysis, six VBM approach, four used DTI technique, one a PET study and eight used an fMRI approach. Two articles that used a multimodal neuroimaging approach will be explained in the corresponding section (Ferguson et al., 2007; de Ruiter et al., 2012).

3. Neuroimaging studies

3.1. Structural neuroimaging (MRI) studies

Structural neuroimaging studies include morphological methods that involve manual segmentation of the selected structures ($n = 4$) (Brown et al., 1995, 1998; Yoshikawa et al., 2005; Ferguson et al., 2007), VBM ($n = 6$) (Saykin et al., 2003; Inagaki et al., 2007; McDonald et al., 2010; de Ruiter et al., 2012; Koppelmans et al., 2012a; Scherling et al., 2012a) and DTI ($n = 4$) (Abraham et al., 2008; Deprez et al., 2011; de Ruiter et al., 2012; Deprez et al., 2012). First, we will describe the most important features of each MRI study within the corresponding MRI technique group and second, we will summarize common and discordant issues that exist between them.

3.1.1. Volumetric analysis

Volumetric analysis is a non-automated method where one or more experienced evaluators, usually blinded to the participant identity, measure the volume of a lesion, a region of interest or the whole brain observing a MRI scan. In some cases the results include some reliability measures for better consistency of the analysis. Evidence of WM changes in cancer patients exposed to chemotherapy was first described in the nineties (Brown et al., 1995, 1998). These volumetric studies found that patients treated with chemotherapy had more WM hyperintensities (WM lesion volume, WMLV) than control participants (Brown et al., 1995). It occurs shortly after the cessation of chemotherapy but persists at 1 year of follow-up (Brown et al., 1998).

A few years later, Yoshikawa et al. (2005) conducted a cross-sectional hippocampal and whole-brain volume study in long-term survivors (an average of 3 years since surgery) of breast cancer patients treated with chemotherapy (C+, $n = 44$). They compared this cohort with a group of breast cancer patients that did not receive chemotherapy (C−, $n = 33$). Hippocampal volume was analyzed using a manual tracing method including intra-rating and inter-rating reliability measures. No statistically significant differences in hippocampal volume were seen between the two groups after adjusting for age, tumor stage[2], hormonal therapy[3] and postmenopausal state. The authors suggested that other brain regions rather than the hippocampus may be involved in chemotherapy-induced memory impairment.

Ferguson et al. (2007) later conducted a case-control structural MRI study consisting of WM volumetry of monozygotic twins, one of which had breast cancer treated with chemotherapy (less than 2 years before). The twin treated with chemotherapy showed more prominent WM hyperintensities in fluid attenuated inversion recovery (FLAIR) (WMLV) compared to non-treated twin. Volumetric analysis of other brain regions of interest (ROIs) (e.g., hippocampus) was also conducted, with findings demonstrating no consistent pattern of difference between the participants. Thus, this limited but compelling initial evidence suggested that chemotherapy-related brain damage, although diffuse, was mainly focused in WM tracts.

3.1.2. Voxel-based morphometry (T1-VBM)

Voxel based morphometry (VBM) is a fully automated procedure for examining tissue integrity that assesses regional volume and density of brain tissue compartments, unlike morphological methods that involve manual segmentation of selected structures. VBM is a method of quantitatively evaluating tissue changes on a voxel-by-voxel basis to an a priori statistical threshold. Hence, this method provides a theoretically unbiased, comprehensive, and highly reliable assessment sensitive to local changes (Ashburner and Friston, 2000, 2001; Good et al., 2001). For this reason, VBM has now replaced other morphometric methods. Note that voxel-based analysis is an automated method that can be used either with T1-weighted images (T1-VBM) to quantitatively assess GM and WM or with diffusion tensor images (DTI-VBA) to quantitatively assess WM tracts.

A preliminary investigation using T1-VBM in breast ($n = 10$) and lymphoma ($n = 2$) long-term (more than 5 years) cancer survivors treated with chemotherapy compared with healthy matched controls (HC, $n = 12$), revealed diffuse cortical and subcortical WM as well as bilateral neocortical GM volume reductions (Saykin et al., 2003).

A few years later, a cross-sectional T1-VBM study was conducted on breast cancer survivors treated with chemotherapy. These patients were split into 2 main groups: those treated less than 1 year after cancer surgery (C+, $n = 55$) and those treated more than 3 years after surgery (C+, $n = 73$). These groups were each compared to a corresponding group of breast cancer survivors who had

[2] Stage of tumor is based in TNM classification. TNM is a staging system that provides a strategy for grouping patients with respect to prognosis (Singletary et al., 2002). Higher stages implies poor prognosis.

[3] Hormonal therapies for breast cancer patients with positive hormone-receptor (approximately 60% of breast cancer patients) include selective estrogen modulator as tamoxifen and other non-selective estrogen therapy as aromatose inhibitors.

not received chemotherapy (C−, $n = 55$ and $n = 59$ at 1 year or 3 years, respectively) and a healthy control group (HC, $n = 55$ and $n = 37$ at 1 and 3 years respectively) (Inagaki et al., 2007). Neuropsychological assessment was carried out using attention and memory indexes of the Wechsler Memory Scale-Revised (WMS-R). Concerning the 1-year study, the C+ group had less GM in the right middle and superior frontal gyrus (rMFG and rSFG) and the right parahippocampal gyrus (medial temporal lobe, MTL), and less WM in the right cingulate gyrus (rCG), bilateral middle frontal gyrus (bMFG), left parahippocampal (lMTL) and the left precuneus regions compared to the C− group. Reduction in volumes of the rSFG GM and left precuneus WM were significantly correlated with the attention index results, and reduction in volumes of the rSFG and right MTL GM were significantly correlated with the visual memory index scores. In the 3-year analysis no differences between C+ and the C− groups were observed. Surprisingly, the comparison between C+ and HC at 1 and 3 years did not show any significant differences in T1-VBM analysis. One important limitation of this study is that variables including performance status, educational level and hormonal therapy were not well matched between groups. In summary, T1-VBM analysis showed differences in regional brain volume between C+ and C− groups at 1 year study, but these differences were not exhibited between the corresponding groups at 3-year study. Thus, based on these results, regional brain structural changes observed in cancer survivors exposed to adjuvant chemotherapy, may recover over time.

In 2010, McDonald and colleagues reported the first longitudinal prospective structural MRI study using the T1-VBM technique. They included breast cancer patients treated with chemotherapy (C+, $n = 17$) and two control groups: breast cancer patients that had not received chemotherapy (C−, $n = 12$) and a matched healthy control group (HC, $n = 18$) (McDonald et al., 2010). The three groups were evaluated before chemotherapy or any hormonal therapy (baseline), at 1 month and then 1 year after the completion of treatment. T1-VBM analysis was used to evaluate differences between groups and over time (within groups) in GM density. Importantly, there were no between-group GM differences at baseline. The comparison between groups showed differences (decreased density) in the bMFG and bilateral cerebellum at 1 month compared to the baseline of both cancer groups (C+ and C−) relative to HCs and this difference only persisted in bilateral cerebellum regions (bCB) of the C+ group after 1 year of follow-up. One important point is that the comparison between C+ and C− group showed no differences at 1 month nor at 1 year (see Fig. 1). In addition, C+ group showed a significant decrease in regional GM density from baseline to 1 month, persisting at 1 year in the bMFG and bilateral superior frontal gyrus (bSFG), bCB regions and right thalamus (see Fig. 2a). These findings are consistent with an acute (1 month) effect of chemotherapy in GM density with subsequent partial recovery over time. Nevertheless, this study had some limitations. While comparison between groups showed interesting differences between C+ and HC group, this difference disappeared when comparing C+ and C− groups. Notably, these results provided the first longitudinal preliminary structural neuroanatomic basis for chemotherapy-related cognitive impairment.

Following this line, de Ruiter and colleagues (de Ruiter et al., 2012) investigated the late effects (more than 9 years) of adjuvant chemotherapy in breast cancer survivors (C+, $n = 17$) compared to non-treated breast cancer patients (C−, $n = 15$). A multimodal MRI study including T1-VBM, DTI, fMRI and single voxel proton MR spectroscopy (MRS) was carried out. T1-VBM demonstrated a reduction of GM volume in the C+ group in posterior parts of the brain: the left lateral posterior parietal cortex (PPC), bilateral precuneus, left occipital cortex and bCB (predominantly left hemisphere), compared to C− group.

Two more T1-VBM cross-sectional studies were published last year. The first study compared breast cancer patients (C−, $n = 23$) with matched healthy controls (HC, $n = 23$) prior to initiation of chemotherapy (Scherling et al., 2012a). A whole-brain and a GM and WM Region of Interest (ROI) analysis were performed. This study revealed smaller pre-chemotherapy WM volumes in C− patients compared to HC in widespread regions in the frontal, parietal and limbic regions using WM ROI analysis. In conclusion, this paper provides preliminary but compelling evidence of neuroanatomical differences between cancer patients and controls prior to chemotherapy. The second study examined long-term (more than 20 years) breast cancer survivors treated with chemotherapy (C+, $n = 184$) compared to nearly 300 matched healthy controls (Koppelmans et al., 2012a). The authors encountered that C+ had significantly less total brain volume and GM volume than HC. No differences were found in WM total brain volume or hippocampal volume. However, this lower widespread GM volume of C+ compared to HC although significant was very small (−2.9 ml of GM volume). Authors compared this volume difference with the effect of 4 years of aging on GM volume in healthy population. Importantly, a non-chemotherapy cancer control group was not included in the study, therefore limiting the delineation of the long-term chemotherapy effect on cognition. In addition, analysis of volumes were not corrected for multiple comparisons. Hence, the conclusions of this study must be considered with caution.

3.1.3. Diffusion-tensor imaging (DTI)

DTI allows the investigation of tissue microstructure and brain connectivity based on the diffusion of water molecules in different directions in brain tissue (Le Bihan et al., 2001). Based on the magnitude of diffusion of water molecules some indices provide details on the underlying microstructure, such as fractional anisotropy (FA) or mean diffusivity (MD). These measurements are mainly used in the articles analyzed in this review in order to provide an index of the integrity of WM. FA, a measure of the directionality of diffusion, has been shown to mirror axonal microstructure in vivo (e.g., axon size, extent of myelination, etc.) (Basser and Jones, 2002). Thus, it has been used to describe the quality of axonal connectivity (Waxman and Bennett, 1972), which in turn might constrain the activity within the connected brain regions and the corresponding cognitive functions (Fonteijn et al., 2008). FA values range from 0 to 1, with values closer to 1 indicating greater uniformity of fiber orientation, which suggest greater WM integrity. Complementary to FA, MD quantifies the overall diffusion in a voxel or region. In this index lower values imply more WM integrity. Other common DTI indexes are: radial diffusivity (RD), also known as perpendicular diffusivity, that measures the diffusivity perpendicular to the principal diffusion direction, and parallel diffusivity, also known as axial diffusivity (PD or AD), that measures the diffusivity parallel to the principal diffusion direction (Pierpaoli et al., 1996; Basser and Pierpaoli, 1996; Le Bihan et al., 2001). Although the biological basis of these measures are complex, decreases in AD are interpreted as axonal injury whereas increases in RD are linked to myelin injury (Budde et al., 2009; Song et al., 2002, 2005). DTI can be analyzed using VBA or using a track-based spatial statistics (TBSS) approach (Smith et al., 2006). This new method was developed to overcome some limitations related to the classical VBA approach: firstly the existence of biased results by the use of standard registration algorithms and secondly the arbitrariness of the choice of the spatial smoothing extent (Smith et al., 2006). In summary, DTI studies are very useful for providing information of subtle changes in WM which could be associated to the cognitive complaints of patients reported after standard chemotherapy treatment.

According to our research, only four studies have used this approach. First evidence demonstrated less WM integrity in DTI studies of cancer patients treated with chemotherapy compared

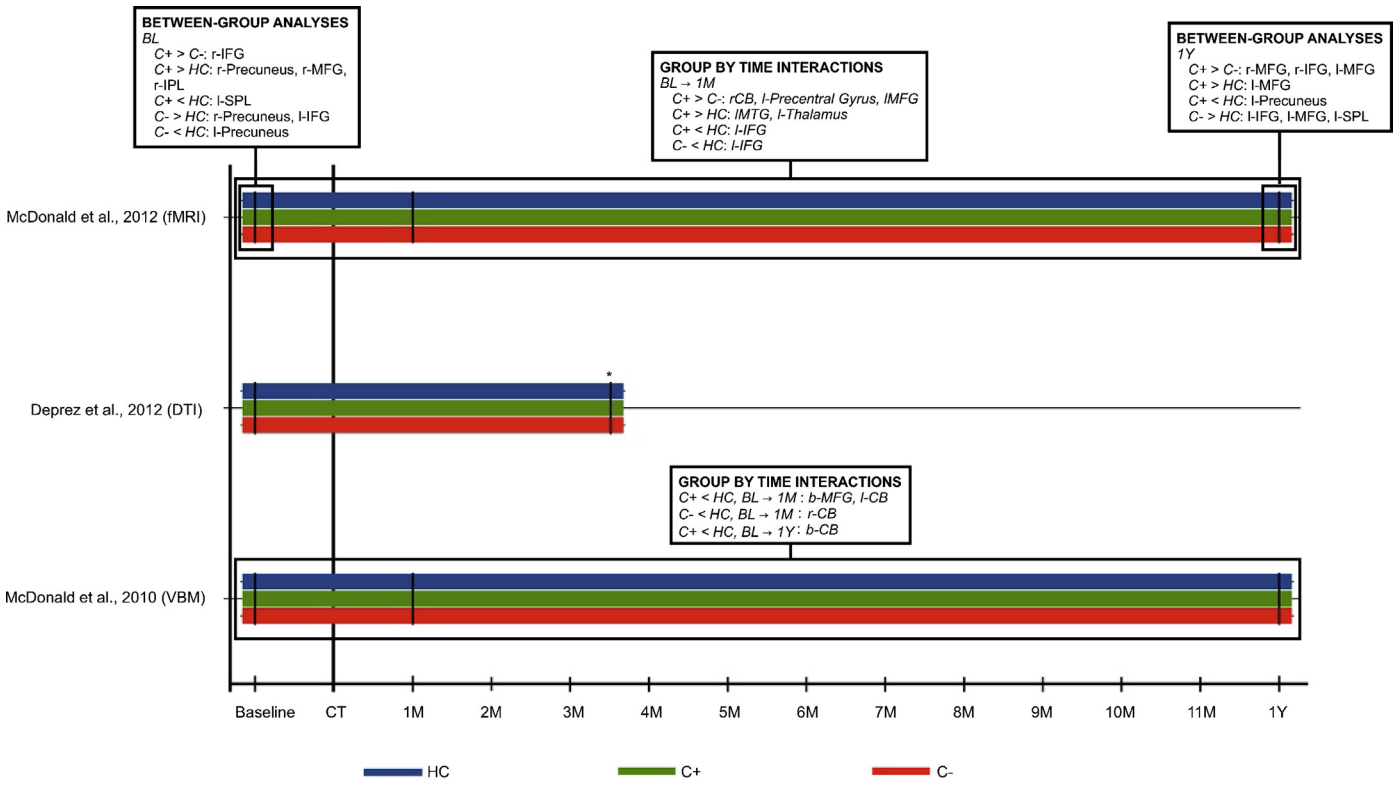

Fig. 1. Graphical representation of the longitudinal studies. Groups are represented by the horizontal bars; time is represented on the horizontal axis. The studies are represented at the vertical axis. BL, baseline; CT, chemotherapy; M, month; Y, year; C+, breast cancer patients following chemotherapy group; C−, breast cancer patients control group; HC, healthy control group; b, bilateral; l, left; r, right; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobule; SPL, superior parietal lobule; CB, cerebellum; MTG, middle temporal gyrus. *Represented as the middle point of the temporal window from 3 to 4 months after completion of chemotherapy treatment. *Note*: All but one longitudinal study (Brown et al., 1998) are represented in the graphic and only the between-group analysis and group by time interactions are described. Brown et al. (1998) study was not included in the graphic because it lacks a control group.

to controls (Abraham et al., 2008). This DTI pilot study compared breast cancer patients (C+, $n = 10$) treated with adjuvant chemotherapy, on average, 2 years (range 3–34 months) after the treatment to a group of matched healthy controls (HC, $n = 10$). Participants completed a digit symbol test (DST) to measure processing speed. FA was analyzed in the genu and splenium of the corpus callosum (CC). The CC is the largest WM bundle in the brain and has been widely used as an index of changes of cerebral WM. C+ group showed slower processing speed and lower FA in the genu of the CC compared to the HC group. As expected, processing speed was positively correlated with FA in the genu. Thus, this study demonstrated decreased integrity of the genu of the CC using DTI in the C+ group associated with a poorer performance in processing speed.

A few years later, Deprez et al. (2011) examined cerebral WM integrity in breast cancer patients treated with chemo less than 6 months before (C+, $n = 17$), comparing the results to a healthy control group (HC, $n = 18$) and a non-chemo treated cancer group (C−, $n = 10$). Differences in DTI-WM integrity parameters were

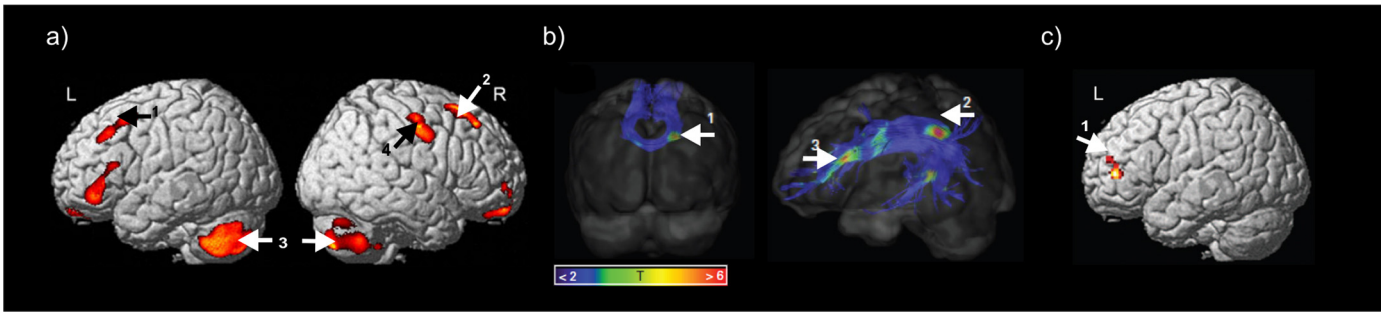

Fig. 2. Longitudinal magnetic resonance imaging (MRI): changes over time in chemotherapy (C+) groups. (a) Longitudinal voxel-based morphometry (T1-VBM) results (C+ group, within-group study over time). C+ showed a significant decrease of GM density from baseline to 1 month persisting at 1 year in the bMFG (see arrow 1 and 4) and bSFG (see arrow 2), bilateral cerebellar regions (bCB, see arrow 3) and right thalamus (adapted from McDonald et al., 2010, with permission of the authors). (b) Longitudinal diffusion tensor imaging (DTI) results (C+ group, within-group study over time). C+ showed a significant decrease in FA between baseline and 3–4 months of follow-up in widespread regions of the corona radiata (CR) and corpus callosum (CC), frontoparietal (superior longitudinal fasciculus, SLF) and occipital (forceps major). It is displayed in a *t*-map overlaid on reconstructed white matter tracts of the CC, SLF and forceps major. The arrows indicate the significant regions, (1) cluster covering parietal part of the CR and CC, (2) cluster covering parietal part of the SLF, and (3) a cluster covering the frontal part of the SLF (adapted from Deprez et al., 2012, with permission of the authors). (c) Longitudinal functional MRI (fMRI) results (C+ group within-group study over time). Both cancer groups (C+ and C−) showed a significant decrease in regional activation between baseline to 1 month that recover (return to the baseline hyperactivation) at 1 year of follow-up. C+ group showed this pattern of change over time especially in the inferior frontal cortex (IFC, see arrow 1) (adapted from McDonald et al., 2012, with permission of the authors).

calculated and assessed using VBA cross-sectional analysis. Cognitive evaluation consisted of a test battery covering several domains. Surprisingly, 7 of the 17 C+ patients (nearly 40%) had cognitive impairment. C+ group demonstrated decreased FA in frontal and temporal WM tracts and increased MD in frontal WM compared to both control groups. Additionally, RD values for the above reported regions were significantly higher in C+ patients than in controls. No significant differences were found in PD values between the groups. These results would suggest demyelinating (RD index) rather than axonal damage (PD index). Attention and processing speed correlated with FA in temporal parts of the inferior and superior longitudinal fasciculus (ILF and SLF) and parietal (SLF, posterior thalamic radiation) WM tracts. The cognitive impaired C+ group showed significant lower FA values than the unimpaired group. In summary, this cross-sectional study demonstrates that DTI-WM integrity parameters provide a sensitive tool to detect neural changes related to chemotherapy-associated cognitive impairment.

The same group (Deprez et al., 2012) published the longitudinal assessment (at baseline and 3–4 months later) of breast cancer patients treated with chemotherapy (C+, $n = 34$), breast cancer patients not exposed to chemotherapy (C−, $n = 16$) and age-matched healthy controls (HC, $n = 19$). Because groups differed significantly in terms of depression score at baseline it was included as a covariate. At baseline there were no differences between the 3 groups for the different neuropsychological tests and FA values. In the longitudinal assessment (at 3 months compared to baseline) only the chemo group showed significant differences. They exhibited a worsening of attention, psychomotor speed, verbal learning and memory in the behavioral study and a significantly decreased FA in widespread regions of the corona radiata (CR) and CC, frontoparietal (SLF) and occipital (forceps major). No changes were found in behavioral assessment or FA in both control groups. In addition, worsening in attention and verbal memory performance correlated with decreased FA in the identified regions. This first longitudinal DTI study showed a clear decrease in WM integrity parameters as well as a correlation of these findings with a worsening in attention and verbal memory, suggesting that microstructural changes in WM underline cognitive changes in chemotherapy-treated patients (see Fig. 2b).

Last, de Ruiter et al. (2012) investigated the late effects (more than 9 years) of adjuvant chemotherapy in breast cancer survivors (C+, $n = 17$) compared to non-treated breast cancer patients (C−, $n = 15$). As mentioned above, a multimodal MRI including T1-VBM, DTI and single voxel proton MR spectroscopy (MRS) were used. The comparison of the mean of DTI values of the entire WM skeleton of the C+ compared to C− group resulted in a significant increase of MD, RD and AD in C+ group. The FA mean yielded no significant differences between groups. However, the TBSS analysis indicated lower focal FA values in the left anterior CR, left external capsule, left sagittal stratum (lSS) (including ILF and inferior fronto-occipital fasciculus), and bilateral posterior thalamic radiation for the C+ group compared to the C− group. For MD, the effects were more widespread than for FA and significant increases in C+ group compared to C− group were present in extensive WM tracts (bilateral retrolenticular part of the internal capsule, bilateral posterior thalamic radiation, bilateral SS, right posterior limb of the internal capsule, bilateral anterior CR, bilateral superior CR, bilateral SLF and the body and genu of the CC). Finally, increases in RD in the C+ compared to the C− group were present in similar regions as the decreases in FA. Thus, these results suggests that both an axonal and a demyelinating degeneration (based on mean DTI values) but with a demyelinating preference (based on an increase RD in TBSS analysis), might underlie the chemotherapy-induced cognitive impairment.

In addition, this multimodal study also included a single voxel proton spectroscopy MR analysis; a non-invasive analytical technique that has been used to study metabolic changes in the brain. Spectroscopy analysis was focused in the centrum semiovale for being a region that contains WM and has a good signal-to-noise ratio. de Ruiter et al. (2012) did not found significant differences in absolute concentrations of metabolites (including N-acetylaspartate or NAA, choline or Cho, creatine or Cr) between groups, however, the C+ group showed a reduction of the ratio NAA/Cr in the left centrum semiovale (including parts of the superior and posterior CR and SLF tracts). The relative reduction of NAA in centrum the semiovale, a metabolite that is localized exclusively in neurons, suggests that axonal degeneration contributed to the observed diffusion abnormalities.

3.1.4. Summary of structural MRI studies

Preliminary studies suggested that chemotherapy-induced cognitive impairment had a widespread rather than a focal neural pattern of affection. T1-VBM studies resulted in a diffuse decrease of GM and WM pattern after chemotherapy treatment that in all but one study (Inagaki et al., 2007) trend to a partial or complete permanence after the cessation of treatment (see Fig. 1 and Table 1).

The different methodologies used in these six T1-VBM studies limit comparisons between them. Only one study was longitudinal (McDonald et al., 2010) and more than a half of the studies had small sample sizes ($n = 12$–17) (Saykin et al., 2003; McDonald et al., 2010; de Ruiter et al., 2012). However, large sample sizes as in Koppelmans' study (Koppelmans et al., 2012a) do not necessarily imply a large effect size.[4] Therefore, we calculated the *Cohen's d* (Cohen, 1988), an effect size measure, of this study and it indicated that despite the fact that differences between groups were significant, the effect size was small.

Chemotherapy regimens were heterogeneous within the studies (Saykin et al., 2003; McDonald et al., 2010; Inagaki et al., 2007) and hormonal therapy was administered in varying proportions among the studies. Comparison of the results using two control groups, C− and HC, was completed in just two studies (Inagaki et al., 2007; McDonald et al., 2010). This is a relevant issue because comparisons with C− or HC groups may result in different outcomes. For example, in the Inagaki et al. study only the comparison between C+ and C− group showed significant differences while only the comparison of the C+ with the HC group showed significant differences in the McDonald et al. study.

Another limitation of all the aforementioned studies is that only two of them had a pretreatment evaluation and interestingly, they resulted in contradictory results. While the longitudinal T1-VBM study showed no differences between groups at baseline (McDonald et al., 2010), the cross-sectional study found a widespread decrease in WM volume of cancer patients compared to the controls (Scherling et al., 2012a). This widespread WM decrease is supported by several neuropsychological studies describing a deficit in processing speed in patients prior to chemotherapy (Wefel et al., 2004), suggesting that cancer itself might have a negative effect on cognitive processing.

DTI studies, in concordance with structural T1-VBM studies, showed the existence of a widespread lower WM integrity with a demyelinating preference damage shown by the diffuse affection in DTI indexes in frontotemporoparietal regions. Long-term follow-up studies demonstrated the persistence of this WM pattern over time (Deprez et al., 2011, 2012; Abraham et al., 2008; de Ruiter et al., 2012). In addition, the comparison between different control

[4] *Effect size* is a measure of the strength of a phenomenon or the degree to which a null hypothesis is false (Cohen, 1988). Thus it is independent of the sample size. For this reason, it is usually employed in meta-analysis.

Table 1
Review of structural cross-sectional MRI studies.

	Time (years)	C+	MRI		
		n	Method	Results	
				HC	C−
Brown et al. (1995)	<1	13	WM volume	WMLV (C+ > HC)	–
Yoshikawa et al. (2005)	3	44	Hippocampal volume	–	ns
Ferguson et al. (2007)	<2	1	WM volume	WMLV (C+ > HC)	–
Saykin et al. (2003)	<5	12	VBM	GMV/WMV (C+ < HC)	–
Inagaki et al. (2007)	<1	55	VBM	ns	GMV (C+ < C−): r-MFG, r-SFG, r-MTL WMV (C+ < C−): r-CG, b-MFG, l-MTL, l-Precuneus
	<3	73		ns	ns
de Ruiter et al. (2012)	<9	17	VBM	–	GMV (C+ < C−): l-LPPC, b-Precuneus, l-Occipital Cortex, b-CB
Scherling et al. (2012a)	Prior	23[a]	VBM	WMV (C− < HC)	–
Koppelmans et al. (2012)a	<20	184	VBM	TBV, GMV (C+ < HC)	–
Abraham et al. (2008)	2	10	DTI-VOI	FA (C+ < HC): genuCC	–
Deprez et al. (2011)	<1	17	DTI-VBA	Same areas as C+ vs. C−	FA (C+ < C−): SFOF, Internal Capsule, CR, ILF, IFOF MD (C+ > C−): SLF, CR, CC, Cingulum RD (C+ > C−): Same areas of FA
de Ruiter et al. (2012)	<9	17	DTI-TBSS	–	FA (C+ < C−): l-CR, l-External Capsule, l-SS, b-Thalamic MD (C+ > C−): b-CR, b-Internal Capsule, b-Thalamic, b-SS, b-SLF, CC RD (C+ > C−): Same regions as FA and Internal Capsule

Groups: C+: chemotherapy group; C−: cancer patients non-treated with chemotherapy; HC: matched healthy controls. *MRI*: magnetic resonance imaging; WM: white matter; VBM: voxel-based morphometry; DTI: diffusion-tensor imaging; DTI-VOI: diffusion-tensor imaging-volume of interest; DTI-VBA: diffusion-tensor imaging-voxel-based analysis; DTI-TBSS: diffusion-tensor imaging-Track-Based Spatial Statistics. *Results*: WMLV: White matter lesion volume; GMV: Gray matter volume; WMV: White matter volume; TBV: total brain volume; FA: fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity. *Regions*: b, bilateral; l, left; r, right; MFG, middle frontal gyrus; SFG, superior frontal gyrus; MTL, medial temporal lobe; CG, cingulate gyrus; LPPC, lateral posterior parietal cortex; CB, cerebellum. *WM tracks*: genuCC, genu of the corpus callosum; SFOF, superior fronto-occipital fasciculus; CR, corona radiata; ILF, Inferior longitudinal fasciculus, IFOF, inferior fronto-occipital fasciculus, SLF, superior longitudinal fasciculus; CC, corpus callosum; SS, sagittal stratum.

[a] It refers to cancer patients prior to chemotherapy (C−).

groups showed the same consistent results (Deprez et al., 2011, 2012) (see Fig. 1 and Table 1).

3.2. Functional neuroimaging (MRI) studies

3.2.1. Functional magnetic resonance imaging (fMRI) studies

fMRI allows for non-invasive in vivo localization and measurement of brain activity by detecting associated changes in blood flow. These hemodynamic responses are generated after the performance of a cognitive or motor task, or even at rest. The hemodynamic response is estimated measuring the blood-oxygen level dependent (BOLD) signal of the whole brain or at different regions of interest (ROIs). This functional technique has been widely used in cognitive and cancer research, with a relatively large number of fMRI studies ($n = 8$) particularly in the last two years (Cimprich et al., 2010; Scherling et al., 2011, 2012b; Ferguson et al., 2007; Kesler et al., 2009, 2011; de Ruiter et al., 2011; McDonald et al., 2012).

In this section we will first describe the fMRI studies that investigated differences between cancer patients and controls prior to the initiation of chemotherapy ($n = 4$) (Cimprich et al., 2010; Scherling et al., 2011, 2012b; McDonald et al., 2012). In contrast to the previously mentioned literature which utilized structural MRI, further research has been conducted on pretreatment assessment of cancer patients using an fMRI approach.

Recent fMRI evidence has revealed higher level of activation of the frontoparietal attentional network (FPN) in cancer populations. The first study of Cimprich et al. (2010) investigated verbal working memory in breast cancer patients (C−, $n = 10$) prior to chemotherapy treatment, compared to controls (HC, $n = 9$). The fMRI data revealed greater levels of activation of the right inferior frontal gyrus and the FPN, including the bilateral frontal and parietal regions, in the C− group. One notable limitation is that fMRI analysis was not corrected by multiple comparisons. Nevertheless, this study highlights the importance of obtaining baseline assessments of cancer patients before chemotherapy treatment.

Furthermore, Scherling and colleagues conducted two studies. In the first (Scherling et al., 2011), the authors examined neurofunctional differences in working memory in patients with breast cancer (C−, $n = 23$) compared to controls (HC, $n = 23$) prior to chemotherapy. Concerning fMRI behavioral data, patients made fewer commission errors and were slower than controls. It is probable that patients were more cautious and made more errors of omission. In addition, patients showed increased activation of the left inferior frontal gyrus (lIFG), left insula, bilateral thalamus and right midbrain during the working memory task than the controls. Hence, the authors suggested that patients found the task more challenging than the controls and that this lead to a greater recruitment of brain regions in order to improve task accuracy.

The same group published another fMRI study (Scherling et al., 2012b) with the same cohort of patients focused on a response inhibition (go/no-go[5]) task. Interestingly, C− group showed less neural activity related to response inhibition in the left cerebellar hemisphere than the HC group. However, the fMRI results were significantly influenced by confounding factors, such as Beck Depression inventory score or time since surgery, and the fMRI pattern of neural activity considering this inhibition go/no-go task is

[5] *Go/no-go task*: An executive function inhibition task in which stimuli are presented in a continuous stream and participants perform a binary decision on each stimulus. One of the outcomes requires participants to make a motor response (go), whereas the other requires participants to withhold a response (no-go).

not the typically described pattern that one expects (Simmonds et al., 2008). Nevertheless, this study provided more neurofunctional evidence of differences at baseline between cancer patients and controls and highlighted the importance of monitoring potential confounding variables.

Some other fMRI studies have focused on chemotherapy-associated neurofunctional changes. First evidence from a pair of twins, one with breast cancer treated with chemotherapy and the other without cancer, indicate a broader spatial extent of activation in typical working memory networks (frontoparietal network) of the chemotherapy-treated twin (Ferguson et al., 2007). Later, these findings were confirmed in a larger fMRI study. Kesler et al. (2009) conducted an fMRI study during a verbal memory task (encoding and recall condition) in breast cancer patients treated with chemotherapy (C+, $n = 14$), a mean of 3 years before (range 6 months to 10 years) in comparison to healthy matched controls (HC, $n = 14$). BOLD activation for C+ patients was significantly lower in the prefrontal cortex (PFC) during the memory encoding condition, but they showed significantly greater activation during the recall condition in multiple brain regions. In addition, chemotherapy type predicted activation within the chemotherapy-group. Women who received a metotrexate-based chemotherapy regimen ($n = 5$) showed significantly lower activation than women who received other chemotherapy ($n = 9$) regimens. These results suggested that although C+ patients have a functional deficit related to memory encoding in the PFC, they exhibit an overactivation of brain regions when attempting to recall information. In conclusion, this study suggests some neurofunctional deficits associated with verbal memory, especially in those treated with a metotrexate-based regimen.

de Ruiter et al. (2011) conducted a cross-sectional study of breast cancer survivors almost 10 years after chemotherapy (C+, $n = 19$) compared with non-treated breast cancer patients (C−, $n = 15$). An executive function task involving planning abilities (Tower of London) and an episodic memory task (pair associates) were administered. BOLD activation for the C+ group versus the C− in an ROI analysis showed less activation of the dorsolateral PFC during the executive task and less activation of the MTL during the memory task. Whole-brain analyses demonstrated less activation of the C+ group in the bilateral PPC during both tasks. These findings suggested that there was a task-specific hypoactivation of the dorsolateral PFC and MTL, and a generalized hypoactivation of the lateral PPC encompassing attentional processing. In summary, this study indicated that chemotherapy-associated negative effects on cognitive function and associated regional brain activity persist in breast cancer survivors over 10 years after the completion of adjuvant systemic therapy.

Another fMRI study (Kesler et al., 2011) examined differences in prefrontal regions between breast cancer survivors treated with (C+, $n = 25$) or without (C−, $n = 19$) chemotherapy an average of 4 years before, compared with a healthy control group (HC, $n = 18$). Breast cancer patients, including the C+ and C− group, demonstrated a hypoactivation in the left medial (middle dorsolateral) PFC and premotor cortex (PMC) compared with the HC group. In addition, only the C+ group showed reduced left lateral PFC activation. These findings suggest that the reduction in medial PFC is more closely related to cancer independently, and the reduction in lateral PFC is more closely related to chemotherapy treatment.

Finally, a very recent longitudinal and prospective study of breast cancer patients treated with chemo (C+, $n = 16$) compared to a non-chemo (C−, $n = 12$) and a healthy control group (HC, $n = 15$) revealed interesting findings (McDonald et al., 2012). Chemo patients were evaluated at baseline (before chemotherapy and hormonal therapy) and at 1 month and 1 year after the completion of treatment, with a working memory (N-back task[6]) fMRI. A between group and a within group (overtime) analysis was accomplished. In the between-group analysis at baseline, cancer patients (including the C+ and C−) showed increased BOLD signal bilaterally in PFC regions (hyperactivation) and less activation in the left parietal region, when compared to HC. In addition, C+ group showed less activation in parietal regions compared to HC over all-time points. In the within-group analysis at 1 month, both cancer groups showed a decrease of this bilateral frontal hyperactivation. At one year however, it partially returned to baseline characteristics. Specifically, the C+ group showed this pattern of change over time, especially in the inferior frontal cortex (IFC) with the C− group showing this pattern in the left cerebellum (lCB). In summary, this study confirms the presence of an overactivation of PFC regions in the cancer group prior to any treatment, with an acute (1 month) decrease that returned partially to its initial activation at 1 year in C+. C− patients have a similar but differential pattern of activation over time with particular emphasis in cerebellum regions (see Fig. 2c).

3.2.2. Positron emission tomography (PET)

PET has served as a useful tool in identifying regional brain activity associated with a variety of conditions affecting cognition. Two types of image-based techniques have been used in this setting: positron-emitting water, and positron-emitting glucose analog (using fluorodeoxyglucose (FDG)). Water-PET has mainly been used to measure acute changes in cerebral blood flow that occur while carrying out specific cognitive tasks. FDG-PET has been frequently employed to assess differences in resting brain metabolism occurring between normal and cognitively impaired subjects.

This study describes the first PET studies (using both techniques) of regional brain activity to explore alterations while performing a memory-related task in women who were treated remotely (5–10 years previously) with chemotherapy for breast cancer (C+, $n = 16$), compared to women with breast cancer who were not treated with chemotherapy (C−, $n = 8$) (Silverman et al., 2007). Cognitive assessment was based on a visual memory task (Rey–Osterreith Complex Figure (ROCF) Delayed Recall). Water-PET and FDG-PET were used to study activation during a word-pair association task and metabolism at rest, respectively. Chemotherapy-treated subjects demonstrated an increased activation in the frontal cortex, with a peak in the inferior frontal gyrus (IFG) and posterior cerebellum during a short-term recall task in the water-PET study. There were no differences in resting metabolism (FDG-PET) between groups. Nevertheless, IFG activity was strongly correlated with performance of ROCF-delayed recall test. Patients who did worst in the ROCF test showed less activation in the FDG-PET study. Within the chemotherapy-group, patients who received tamoxifen showed decreased metabolism in the basal ganglia (lentiform nucleus) compared to patients that not received tamoxifen. This was the first PET study to identify a particular PET activation pattern for chemotherapy-treated breast cancer patients especially focused in IFC.

3.2.3. Summary of functional MRI studies

These results suggest the existence of a pretreatment subtle working memory impairment corresponding with a higher level of activation of the FPN, especially in prefrontal regions, of cancer patients compared to healthy controls (Cimprich et al., 2010; Scherling et al., 2011, 2012b; McDonald et al., 2012). Hence, fMRI

[6] *N-back task* is a working memory task that consists of indicating when the current stimulus matches the one from n steps earlier in the sequence. The factor n can be adjusted to make the task more or less difficult.

Table 2
Review of functional cross-sectional MRI studies.

	Time (years)	C+	fMRI/PET results		
		n	Task	HC	C−
Cimprich et al. (2010)	Prior	10[a]	WoM	C− > HC: b-IFG, b-Parietal C− < HC: ACC	–
Scherling et al. (2011)	Prior	23[a]	WoM	C− > HC: l-IFG, l-insula, b-thalamus, r-Midbrain	–
Scherling et al. (2012b)	Prior	23[a]	EF	C− < HC: l-CB	–
Ferguson et al. (2007)	<2	1	WoM	C+ > HC: b-Frontal, b-Parietal	–
Kesler et al. (2009)	3	14	VM	Encoding: C+ < HC: b-SFG, b-MFG, l-precentral gyrus Recall: C+ > HC: r-STG, b-Lingual Gyri, l-MTL, b-BG, r-SFG, b-IFG, MFG and precentral gyrus, r-CG, b-Insula, b-Precuneus, b-Cuneus, CB	–
de Ruiter et al. (2011)	10	19	EF VM	–	C+ < C−: l-PFC, b-PPC C+ < C−: r-MTL, b-PPC
Kesler et al. (2011)	4	35	EF	(C+ and C−) < HC: l-medial PFC and PMC C+ < (HC and C−): l-lateral PFC	
Silverman et al. (2007)[b]	5–10	16	VM	–	C+ > C−: l-IFG, CB, SFG C+ < C−: l-PPC, l-Occipital Cortex, b-CB

Groups: C+: chemotherapy group; C−: cancer patients non-treated with chemotherapy; HC: matched healthy controls. *Task* (*cognitive domain*): WoM: working memory; EF: executive function; VM: verbal memory. *MRI*: magnetic resonance imaging; fMRI: functional magnetic resonance imaging; PET: positron emission tomography study. *Results*: b, bilateral; l, left; r, right; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; CB, cerebellum; SFG, superior frontal gyrus; MFG, middle frontal gyrus; STG, superior temporal gyrus; MTL, medial temporal lobe; BG, basal ganglia; CG, cingulate gyrus; PFC, prefrontal cortex; PPC, posterior parietal cortex; PMC, premotor cortex.
[a] It refers to cancer patients prior to chemotherapy (C−).
[b] PET study.

tasks are more challenging for patients, who need to increase and expand the recruitment of these brain regions to improve task accuracy.

fMRI results after the completion of chemotherapy showed a different chemotherapy neurofunctional pattern. These studies pointed out an early (from months to 1–2 years) working memory related pattern of decreased bilateral frontal activation especially in IFC (McDonald et al., 2012) and a verbal memory recall pattern of increased activation of more widespread regions (Kesler et al., 2009). These earlier changes nearly returned to baseline levels in a longitudinal study after 1 year of treatment (McDonald et al., 2012), but conversely they seem to persist in other long-term follow-up studies. This long-term follow-up (more than 1–3 years) research data showed an hypoactivation of some brain regions, especially the PFC and IFC (Kesler et al., 2009; de Ruiter et al., 2011; Kesler et al., 2011; Silverman et al., 2007), MTL (de Ruiter et al., 2011) and PPC (de Ruiter et al., 2011; McDonald et al., 2012). It is suggested that early brain activation changes may be compensatory in nature, as have been described in other cognitive disease studies as moderate cognitive impairment (Dickerson et al., 2005), while long-term brain hypoactivation changes may correspond to the established cognitive deficits described in long-term cancer survivors (Koppelmans et al., 2012b) (see Table 2).

These studies exhibited some limitations. First, fMRI tasks or cognitive paradigms used were not the same in all the studies, being N-back task the most frequently used (Scherling et al., 2011, 2012b; Ferguson et al., 2007; McDonald et al., 2012). This is a relevant issue as tasks belonging to different neuropsychological domains activate different brain networks. Second, the type of chemotherapy differed between and within the major part of studies with just one exception (de Ruiter et al., 2011). However, this point was only taken into consideration in the Kesler et al. study (2009). Authors demonstrated that chemotherapy type predicted activation within the chemotherapy-group. Although metotrexate is a chemotherapy agent no longer used as standard therapy of breast cancer patients, this study highlights the importance of chemotherapy homogeneity in chemotherapy-related cognitive studies.

3.3. Multimodal MRI studies

Two multimodal MRI studies have been published. The first, by Ferguson et al. (2007) conducted a structural and fMRI study in a pair of twins. This interesting but limited study has been well described in each section. The second study deserves to have a special mention (de Ruiter et al., 2011). Although it is a cross-sectional study of breast cancer survivors treated with high-dose chemotherapy almost 10 years before ($n = 19$) compared with non-treated breast cancer patients ($n = 15$), it is the first study to integrate various MRI modalities. To summarize, T1-VBM showed a reduction of GM volume in C+ group in posterior parts of the brain: the left lateral PPC, bilateral precuneus, left occipital cortex and bilateral CB (predominantly left hemisphere) compared to C− patients. These areas overlap with the fMRI regions on the BOLD contrast images showing hypoactivation during the memory association task. In addition, DTI maps reflecting increases in MD and RD (bilateral posterior thalamic radiation) in the C+ group overlap with the brain regions showing hypoactivation in the fMRI (lateral PPC). DTI parameters (MD and RD) showed a significant negative correlation with NAA/Cr ratio of spectroscopy. In conclusion, these results both suggest that chemotherapy-induced cognitive impairment is related to long-term damage of both WM and GM, and that different neuroimaging approaches, either structural or functional, provide different evidence of converging cognitive processes.

4. Limitations

The neuroimaging studies reviewed above exhibited some important limitations. Mainly, there is a huge heterogeneity concerning the experimental methodology. For this reason, since 2011 the International Cancer and Cognitive Task Force (ICCTF) guidelines recommended longitudinal neuropsychological repeated assessment with pretreatment evaluation, as well as two control groups: disease-specific and a healthy control groups (Wefel et al., 2011). The evaluation of a healthy control group is important for the proper assessment of repetition effects in longitudinal studies or changes in scanner performance over time (Johansen-Berg, 2012).

Moreover, only breast cancer patients' studies were included in the present review. All studies except one (Koppelmans et al., 2012a) had relatively small sample sizes and only three of them were longitudinal (McDonald et al., 2010; Deprez et al., 2012; McDonald et al., 2012). Hence, all these factors limit the generalization of the results and might also explain some of the contradictory results encountered across the studies.

5. Conclusions

The review of the neuroimaging studies in cancer and chemotherapy-treated cancer patients revealed both structural and functional differences and yielded several important points.

First, neuropsychological evidence of a subtle pretreatment cognitive impairment in cancer patients, especially in working memory and processing speed, is in agreement with the described widespread decrease in WM volume (Scherling et al., 2012a) and the overactivation of the FPN compared to healthy controls (Cimprich et al., 2010; Scherling et al., 2011, 2012b; McDonald et al., 2012).

Second, based on this research, chemotherapy treatment causes several neural changes that contribute to a well-defined structural and functional cognitive impairment pattern. Structural and functional studies converge in showing an early diffuse pattern of affection consisting of a decrease in volume of GM and WM (Inagaki et al., 2007; McDonald et al., 2010; Deprez et al., 2011, 2012) and a frontal decrease of the baseline overactivation of the FPN (McDonald et al., 2012). This pattern partially returns to baseline levels according long-term follow-up studies, with a persisting decrease in GM and WM volumes in a subgroup of patients (Saykin et al., 2003; Inagaki et al., 2007; McDonald et al., 2010; de Ruiter et al., 2012; Koppelmans et al., 2012a) together with a predominantly frontal cortex hypoactivation (Kesler et al., 2009, 2011; de Ruiter et al., 2011; Silverman et al., 2007).

Finally, although research in this field has greatly increased in the last two or three years, there is a considerable need for further investigation in this area with well-designed prospective studies to clearly elucidate the mechanisms underlying theses neural changes.

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