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REVIEW

The Developmental Trajectory of Cancer-Related Cognitive Impairment in Breast Cancer Patients: A Systematic Review of Longitudinal Neuroimaging Studies

Helena Sousa[1,2] · Susana Almeida[2,3] · João Bessa[2,4,5] · M. Graça Pereira[1,2]

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Abstract

This systematic review explored the neurobiological mechanisms underlying the clinical time course of cancer-related cognitive impairment (CRCI) in breast cancer patients through the review of longitudinal neuroimaging studies. Before chemotherapy, results reported no evidence for neuropsychological, structural (gray matter) and brain perfusion changes. However, functional brain alterations were evident and revealed a frontoparietal hyperactivation during working memory tasks. Fatigue and number of days since surgery were the two suggested confounding factors. Acutely after chemotherapy, this review found no evidence for neuropsychological changes while suggesting a pattern of frontal structural, perfusion and functional brain abnormalities. These findings seemed to be dependent on age, menopausal status at baseline, and fMRI task performed. Years after chemotherapy, results revealed evidence of partial neuropsychological, structural, and functional brain recovery. Regarding brain abnormality, this review suggested that it may begin quite early in the disease course, be more prominent shortly after chemotherapy and partially recover over time. Several hypotheses underlying these changes were discussed. The present review also provided important information for developing a time-specific treatment and prevention strategies and for the consideration of functional neuroimaging as a relevant tool for CRCI diagnosis, clinical monitoring, and intervention studies. The findings also suggested the need to implement studies with longitudinal designs, including a pre-treatment assessment, since cross-sectional studies were not able to detect this pattern of recovery over time, supporting only the theory of brain abnormalities, in breast cancer survivors.

Keywords Breast cancer · Cognition · Cancer-related cognitive impairment · Neuroimaging · MRI · fMRI

Introduction

Cancer-related cognitive impairment has become a major area of concern for patients and physicians because of its consequences on well-being, quality of life, functional autonomy, and treatment decision-making (Castellon & Ganz, 2009; Klemp et al., 2018; Wefel, Saleeba, Buzdar, & Meyers, 2010). However, it is one of the most controversial side effects in the literature and in clinical practice.

Initially, these cognitive changes were theorized at the psychosocial level and attributed to cancer-related distress, anxiety, depression, or fatigue. With studies statistically controlling these variables and indicating that most cancer patients had no clinically significant psychological symptoms (Ahles & Saykin, 2007), a pharmacological perspective was then assumed. Next, the term "chemobrain" was adopted, suggesting that cognitive changes were induced by chemotherapy. However, emerging data are challenging this concept, confirming that a subset of patients have cognitive impairment

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✉ M. Graça Pereira
gracep@psi.uminho.pt

[1] Family Health & Illness Research Group, School of Psychology, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal

[2] Research Center in Psychology (CIPsi), School of Psychology, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal

[3] Psycho-Oncology Service, Portuguese Institute of Oncology, Porto, Portugal; Cuf Hospital, Porto; Faculty of Medicine, University of Porto, Braga, Portugal

[4] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

[5] ICVS/3B's - PT Government Associate Laboratory, Guimarães, Braga, Portugal

before the beginning of the treatment (Berman et al., 2014; Cimprich et al., 2010; Kesler et al., 2017a; Menning et al., 2015; Scherling, Collins, MacKenzie, Bielajew, & Smith, 2011). As a consequence, the term "chemobrain" is no longer suitable and has been altered to a more general concept: Cancer-Related Cognitive Impairment (CRCI; Deprez et al., 2018; Wefel, Vardy, Ahles, & Schagen, 2011).

The neural mechanisms underlying these cognitive changes have been the subject of increasing research, with several cross-sectional studies supporting structural and functional brain abnormalities o following chemotherapy, and particularly in long-term survivors (Conroy et al., 2013b; Kesler et al., 2013; Koppelmans, Breteler, Boogerd, Seynaeve, & Gundy, 2012a; Miao et al., 2016; Stouten-Kemperman et al., 2015). However, the cross-sectional methodology is susceptible of a high rate of error and bias and is insufficient to demonstrate the course of brain changes throughout the disease process. Therefore, the interpretation of the results of the reported studies is limited because differences between the groups exposed to systemic treatment and healthy controls do not necessarily reflect the changes caused by the treatment (Deprez et al., 2018; Wefel et al., 2011).

The present systematic review aims to explore the neurobiological mechanisms underlying the clinical course of CRCI, focusing on longitudinal neuroimaging studies with breast cancer samples. The findings will be discussed considering the course of brain changes and, therefore, organized from pre- to post-treatment.

Hereafter, the authors will adopt the terminology commonly found in the revised studies to facilitate understanding of the differences in the sample, referring to breast cancer patients who underwent chemotherapy as "C+" and to breast cancer patients who did not undergo chemotherapy as "C-". Healthy controls will be acknowledged as "HC".

Methods

The reviewers established the protocol for this systematic review in line with the guidelines of The Cochrane Collaboration Manual (Higgins & Green, 2008). The findings were reported using the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009).

Eligibility Criteria

Eligibility criteria were established according to the PICOS structure (Liberati et al., 2009; Moher et al., 2009) and considering the International Cognition and Cancer Task Force (ICCTF) recommendations for the study of CRCI (Deprez et al., 2018; Wefel et al., 2011). Subsequently, studies were included based on the following criteria:

• *Population*: group of women diagnosed with early stage breast cancer (from stage 0 to stage III). No menopausal status or age restrictions were considered. The choice of this population took into account the fact that very limited data are available with non-central nervous system patients, other than women with breast cancer. Considering other diagnosis would not allow comparisons, since treatment regimens, agents and doses vary widely and, consequently, imply different side effects. Patients with advanced cancer stages were also excluded, since there is the possibility of brain metastasis.

- *Interventions:* exposure to chemotherapy. No restrictions were applied regarding the presence or absence of other adjuvant treatments.
- *Comparator*: healthy-matched controls or disease-specific controls, as recommended by ICCTF. This approach can help establish whether the brain changes are present or whether apparent changes are due to practice, to treatment regimens or to cancer itself.
- *Outcomes:* the primary outcomes are the brain changes assessed through brain-based neuroimaging techniques, since neuroimaging techniques may be more sensitive than neuropsychological tests to reveal CRCI (Deprez et al., 2014).
- *Study designs:* longitudinal studies that include a baseline assessment (prior to chemotherapy).

Studies were excluded if not published in English or in a peer-reviewed journal. Thesis and conference abstracts were not considered. No limits were applied to publication date.

Information Sources

Studies were identified by searching four electronic databases starting with PubMed, followed by Web of Science, ScienceDirect and PsycInfo. Last search was performed in August 28th 2018. Electronic searches were supplemented by tracking citations.

Search

The search strategy begun with the identification of the main terms based on PICOS: "breast cancer", "cognition" and "neuroimaging". Secondly, the authors identified synonyms and consulted medical descriptors (e.g. MeSH terms). The following search terms were used: "breast cancer OR breast neoplasm OR breast carcinoma" AND "cognition OR cognition disorders OR cognitive dysfunction OR cognitive impairment" AND "neuroimaging OR magnetic resonance imaging OR functional neuroimaging OR neuroimaging methods".

The search limits were applied for title/abstract, English language and peer-reviewed journals, when the option was

available. For more information about the detailed research process, see Appendix 1.

Study Selection

Data extraction from databases was performed by one author (HS), while eligibility assessment was performed independently by two authors (HS and SA). All unique papers were organized into a Microsoft Excel spreadsheet. Studies were screened for eligibility over three steps: (1) labelled as included, excluded, or unclear, based on title and abstract; (2) those papers labelled as included and unclear were then retrieved, and (3) the full text was reviewed, in both situations.

Data Collection Process

The data collection process was made by one author (HS), while two authors (SA and JB) confirmed all the data extracted. All data were collected directly from the published papers into a Microsoft Excel spreadsheet. A few contacts were made for data clarification when needed.

Risk of Bias in Individual Studies

Critical appraisal of the selected studies was performed using PRISMA recommendations (Moher et al., 2009) while consulting the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for Case-Control Studies 2017, an evidence-based organization that developed guidelines to correctly conduct critical appraisals for systematic reviews (Munn, Moola, Riitano, & Lisy, 2014).

Two reviewers conducted the appraisal and its ratification (HS and JB). Discrepancies were resolved by discussion and consensus. For more information about risk of bias assessment, see Appendix 1.

Results

Study Selection

Database search provided a total of 160 records while four additional records were retrieved from checking reference lists. After duplicates removal, 110 studies remained for further examination. From these, 93 were excluded because they did not meet the inclusion criteria. After this procedure, 17 studies remained for further examination and were checked for repeated samples and repeated data. Duplications were searched based on the name of the first author of each article, all the names of the co-authors, date of publication, place of recruitment, applied tasks and patients' characteristics. After this process, 15 papers were categorized as duplicates resulting in the exclusion of one paper (Deprez et al., 2012), since the results were reported in another study (Billiet et al., 2018). The other overlapping papers were kept in the present review since they described different outcomes for the same sample. In this case, the strategy adopted was to synthesize the evidence was the combination of the findings. The determination of duplicates was performed by one author (HS) and confirmed by a second author (SA). Both authors followed the recommendations published by Dijkers (2018).

To this end, a total of 16 studieswas reviewed and included. Figure 1 presents the different stages of study selection (cf. Prisma Flow Diagram).

Studies Characteristics

The 16 included studies were published from 2010 to 2018. Patients were from the United States (n = 11), Belgium (n = 2), the Netherlands (n = 2) and Canada (n = 1). Ten studies had two control groups comparing breast cancer patients who received chemotherapy (C+) with healthy controls (HC = women without cancer) and breast cancer patients who did not receive chemotherapy (C-). The remaining six studies, only performed healthy control comparisons.

All studies had at least two assessment time points. The pre-treatment evaluation took place after surgery, but before the start of adjuvant treatments (time point 1 or baseline). Only one study performed a pre-surgery assessment (Kesler et al., 2017b). Follow-up assessments (time point 2) were performed one to six months after chemotherapy. Six studies had a third follow-up moment, ranging from 7 months to 3–4 years after chemotherapy (time point 3). Controls were assessed at matched intervals.

Patient Characteristics

This review comprises a total of 949 female participants. From this total, 361 were C+ patients, 226 were C- patients and 362 belonged to the HC group.

Sociodemographic characterization revealed that the C+, C- and HC patients had an average age of 50.8, 50.6 and 51.5 years old, respectively. Participants were matched by age and education level. Available data suggested that the mean level of education ranged from 14.8 to 16.9 years for patients with C+, from 14.6 to 16.1 for patients with C- and from 15.1 to 17.6 for HC.

Clinical characterization revealed that 28% of C+ patients were in stage I, 56.8% in stage II and 15.2% in stage III breast cancer. Patients from the C+ group were treated with standard-dose polychemotherapy regimens, with the majority of patients receiving a combination of three cytotoxic agents: doxorubicin (anthracyclines agent), cyclophosphamide (alkylating agent) and paclitaxel (taxane). Two papers (McDonald, Conroy, Smith, West, & Saykin, 2013; Nudelman et al., 2014) included patients who underwent

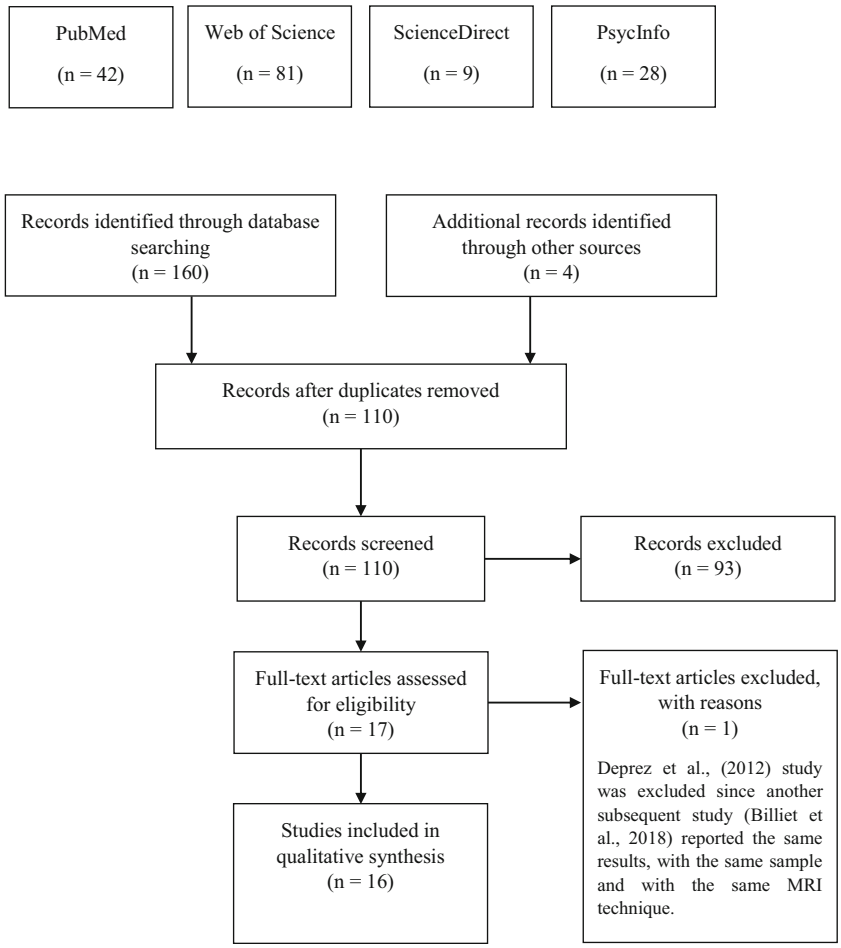

Fig. 1 PRISMA flow chart for study inclusion

primary chemotherapy (before surgery), representing only 4% of all the C+ patients.

Psychological Assessment

Anxiety (n = 12), fatigue (n = 6) and worry (n = 2) were the most commonly evaluated domains. Table 1 presents all the domains assessed, patient-reported outcome measures applied and major results. Most studies reported that there were no between-group differences at any time point for anxiety and depression. All mean scores were below clinical thresholds, indicating that participants in C +, C- and HC did not show clinically significant symptoms of depression or anxiety throughout the studies.

Regarding fatigue, the results suggested clinically significant symptoms in the C+ group at baseline and after chemotherapy (Askren et al., 2014; Menning et al., 2017; Menning et al., 2018; Zunini et al., 2013).

Neuropsychological Assessment

Nine studies used pen and paper or computerized neuropsychological tools to assess cognition (n = 3). Three studies used neuropsychological test batteries (Chen et al., 2018a, 2018b; Nudelman et al., 2014), while the remaining publications applied domain-specific measures.

A total of nine cognitive domains was analyzed and 20 different measures were applied. Memory (n = 8), processing speed (n = 8), attention (n = 6), and executive functioning (n = 5) were the most evaluated cognitive domains across studies. Memory was frequently subdivided in its many forms: visual memory (n = 4), working memory (n = 4), verbal memory (n = 4), and episodic memory (n = 2). Table 2 presents the several domain-specific measures used in the included papers.

At baseline (time point 1), the results from the neuropsychological assessments revealed that only one study showed significant differences between C+ and HC (Kesler et al., 2017b). These differences were found in domains such as verbal fluency, verbal memory, attention, processing speed, and executive functioning.

After chemotherapy, only one study (Billiet et al., 2018) reported significant between-group differences by revealing that C+ patients had lower cognitive performance in attention, processing speed and memory tests when compared to HC. Although not significant, Lepage et al. (2014) found an overall decline for all cognitive domains assessed in the C+ group

Table 1 Psychological domains assessed, measures applied and major results

References	Domain	Measures	Major findings
Askren et al., 2014	Depression Fatigue Worry	PHQ-8 FACIT-F TIWI	• Depression was not clinically significant; no differences between groups at any time-point; • At T1: 32% C+ vs 15% C- and HC had significant fatigue. At T2: 52% C+ vs 20% C- and HC.
Billiet et al., 2018	Anxiety Depression Fatigue	STAI BDI FAS	• No clinically significant symptoms; • At all time-points C+ ↑ depression scores.
Conroy et al., 2013a	Anxiety Depression	STAI CES-D	• No clinically significant symptoms; • No between-groups differences at any time-point.
Deprez et al., 2014	Anxiety Depression	STAI BDI	• No clinically significant symptoms; • No between-groups differences reported.
Jung et al., 2017	Depression Worry	PHQ-8 TIWI	• No clinically significant symptoms; • C+ ↑ worry (vs C- and HC) across all time-points.
Kesler et al., 2017b	Depression Anxiety Cognitive Fatigue	CAD	• No clinically significant symptoms; • No between-groups differences at any time-point.
McDonald et al., 2010	Anxiety Depression	STAI CES-D	• No clinically significant symptoms; • No between-groups differences at any time-point.
McDonald et al., 2012	Anxiety Depression Fatigue	STAI CES-D	• No clinically significant symptoms; • No between-groups differences at any time-point.
McDonald et al., 2013	Anxiety Depression	STAI CES-D	• No clinically significant symptoms; • No between-groups differences at any time-point.
Menning et al., 2017	Anxiety Depression Quality of life Symptoms Perceived Stress Trauma Personality	POMS EORTC QLQC-30 HSCL-25 PSS TSQ 10-PI	• No clinically significant symptoms; • Some results were not reported (stress, trauma and personality); • QoL: C+ ↓ physical function and ↑ fatigue than HC at T2.
Menning et al., 2017	Anxiety Depression Quality of life Symptoms Perceived Stress Trauma Personality	POMS EORTC QLQC-30 HSCL-25 PSS TSQ 10-PI	• No clinically significant symptoms; • Some results were not reported (stress, trauma and personality); • QoL: C+ ↓ physical function and ↑ fatigue than HC at T2.
Nudelman et al., 2014	Anxiety Depression	STAI CES-D	• No clinically significant symptoms; • No between-groups differences at any time-point.
Zunini et al., 2013	Anxiety Depression Fatigue Vigor Anger Confusion.	BAI BDI POMS	• C+ ↑ anxiety, depression, anger, confusion and fatigue, and ↓ vigor than HC at both T1 and T2.

C+: women with breast cancer who underwent chemotherapy; C-: women with breast cancer who did not undergo chemotherapy; HC: healthy matched-controls; QoL: quality of life; PHQ-8: The eight-item Patient Health Questionnaire depression scale; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; TIWI: Three Item *Worry* Index; STAI: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory; FAS: Fatigue Assessment Scale; CES-D: Center for Epidemiologic Studies of Depression

compared to HC. A different result was found by Conroy and colleagues (Conroy, McDonald, Ahles, West, & Saykin, 2013a) by demonstrating an overall improvement in all cognitive domains immediately after chemotherapy, except for the post-menopausal group of women.

Only three of the seven studies that performed neuropsychological evaluations had a longer follow-up assessment (time point 3). The results revealed an overall within-group improvement, although significant between-group differences remained. Lepage et al. (2014) found that this improvement

Table 2 Domain-specific measures used in the included papers in this review

Cognitive domain	Neuropsychological tool	References
Attention	CTMT	Kesler, et al., 2017b
	Flanker Task	Menning et al., 2017
		Menning et al., 2018
	TEA	Billiet et al., 2018
	VRT	Menning et al., 2017
		Menning et al., 2018
	WAIS Backward Digit	Billiet et al., 2018
		Menning et al., 2017
		Menning et al., 2018
Learning Memory	RAVLT	Billiet et al., 2018
	RVLT	Billiet et al., 2018
Verbal Memory	CNS-VS verbal memory index	Lepage et al., 2014
	CVLT	Conroy et al., 2013a
	HVLT	Lepage et al., 2014
		Menning et al., 2017
		Menning et al., 2018
	RAVLT	Kesler et al., 2017b
Visual Memory	BLT	Conroy et al., 2013a
	BVMT	Lepage et al., 2014
	CNS-VS visual memory index	Lepage et al., 2014
	WMS-R	Menning et al., 2017
		Menning et al., 2018
Working Memory	ACT	Lepage et al., 2014
	CNS-VS flexibility index	Lepage et al., 2014
	CNS-VS working memory index	Lepage et al., 2014
	COWA	Lepage et al., 2014
	PASAT	Conroy et al., 2013a
		Lepage et al., 2014
	WAIS Digit-Span	Lepage et al., 2014
	WAIS Letter-Number	Lepage et al., 2014
Processing Speed	9-PEG	Billiet et al., 2018
	CNS-VS processing speed index	Lepage et al., 2014
	CNS-VS reaction time index	Lepage et al., 2014
	CTMT	Kesler et al., 2017b
	D-KEFS	Conroy et al., 2013a
	TMT-A	Lepage et al., 2014
		Menning et al., 2017
		Menning et al., 2018
	TMT-B	Lepage et al., 2014
	WAIS Digit-Symbol	Billiet et al., 2018
		Conroy et al., 2013a
		Lepage et al., 2014
		Menning et al., 2017
		Menning et al., 2018
	WAIS Symbol Search	Lepage et al., 2014

Table 2 (continued)

Cognitive domain	Neuropsychological tool	References
Executive Function	BADS	Menning et al., 2017
		Menning et al., 2018
	CTMT	Kesler et al., 2017b
	TMT-B	Menning et al., 2017
		Menning et al., 2018
Distractibility	CPT	Conroy et al., 2013a
Verbal fluency	COWA	Kesler et al., 2017b

CTMT: Comprehensive Trail-Making Test; Flanker Task: Eriksen Flanker Task; TEA: Test of Everyday Attention; TMT: Trail Making Test; VRT: Visual Reaction Time; WAIS: Wechsler Adult Intelligence Scale; RAVLT: Rey-Auditory Verbal Learning Test; RVLT: Rey- Verbal Learning Test; CNS-VS: Central Nervous System Vital Signs, a computerized tool; CVLT: California Verbal Learning Test; HVLT: Hopkins Verbal Learning Test; BLT: Brown Location Test; BVMT: Brief Visuospatial Memory Test; WMS-R: Wechsler Memory Scale Revised; ACT: Auditory Consonant Trigrams Test; COWA: Controlled Oral Word Association Test; PASAT: Paced Auditory Serial Addition Task; 9-PEG: Nine-Hole Peg Test; D-KEFS: Delis–Kaplan Executive Function System; BADS: Behavioral Assessment of the Dysexecutive Syndrome

was significant for processing speed one year after treatment, while Billiet et al. (2018) found that this pattern of improved performance was preserved up to 3–4 years after chemotherapy for verbal memory and processing speed. Nevertheless, Kesler and colleagues (2017b) reported that 59% of the C+ patients had persistent cognitive impairment while 41% had late onset cognitive impairment.

Five out of nine studies revealed significant correlations with brain-based measures. Major results revealed a correlation between attention, memory and processing speed with white matter reductions (Billiet et al., 2018) and lower gray matter volume (Lepage et al., 2014) in several frontal regions of the brain. Table 3 presents the major neuropsychological results and their correlations with brain-based measures.

Subjective Cognition Assessment

Seven studies reported data on patients' subjective cognitive complaints. Four different self-report measures were applied (AFI, CFQ, BRIEF-A and MOS-Cog). Results indicated similar cognitive complaints at baseline for all three groups (C+, C- and HC). After treatment, C+ patients perceived more complaints (Askren et al., 2014; Billiet et al., 2018; Deprez et al., 2014; McDonald et al., 2013; Menning et al., 2018). These complaints were significantly correlated with greater fatigue and depression (Billiet et al., 2018), greater worry and physical symptom severity (Jung et al., 2017), lower brain activation while multitasking (Deprez et al., 2014), higher parietal activation (Menning et al., 2017), and lower grey matter density (McDonald et al., 2013). Table 4 presents the applied subjective cognitive complaints measures, major results, and correlations with brain-based measures.

Brain-Based Measures

Brain-based outcomes were extracted from all the 16 studies. Seven studies assessed changes in brain structure (Billiet et al., 2018; Chen et al., 2018a; b; Lepage et al., 2014; McDonald, Conroy, Ahles, West, & Saykin, 2010; McDonald et al., 2013; Menning et al., 2018), one study assessed brain perfusion (Nudelman et al., 2014) while the remaining eight studies assessed changes in brain activity (Askren et al., 2014; Conroy et al., 2013a; Deprez et al., 2014; Jung et al., 2017; Kesler et al. 2017b; McDonald et al., 2012; Menning et al., 2017; Zunini et al., 2013).

Brain Structure Outcomes

Table 5 presents all brain structure results. These studies employed different techniques to measure structural changes in the brain. Four studies applied voxel-based morphometry (VBM), a technique that allows the measurement of the whole brain volume or its subparts measured by drawing regions of interest (ROIs) and calculating the volume enclosed (Chen et al., 2018a; Lepage et al., 2014; McDonald et al., 2010; McDonald et al., 2013).

One study (Chen et al., 2018b) also measured brain volume using the cloud-based Neuroreader™ software which measures segmented brain structures from magnetization prepared rapid gradient echo (MP-RAGE) sequence. Two studies applied diffusion tensor imaging (DTI) models, an MRI-based technique that has the sensitivity to detect microstructural changes based on water diffusion within the brain (Billiet et al., 2018; Menning et al., 2018). With this technique, brain's white matter fiber tracts can be delineated based on the calculation and analysis of parameter maps, such as those measuring fractional anisotropy (FA), mean diffusivity (MD),

Table 3 Neuropsychological evaluation results and their correlations with brain-based measures

References	Domains evaluated	Major results
Billiet et al., 2018	Attention, concentration, learning memory and processing speed.	• T1: no between-group differences (Deprez et al., 2012); • At T2: C+ ↓ attention, processing speed and memory at T2 (vs C- and HC) (Deprez et al., 2012); • C+ ↓ attention and verbal memory correlated with ↓ WM in frontal and occipital areas (Deprez et al., 2012); • C+ ↓ performance from T1 to T2 and ↑ from T2 to T3; • At T3: C+ increased performance in verbal memory and processing speed; • Brain-based FA changes followed the same trend.
Chen et al., 2018a	Attention, episodic memory, working memory, processing speed, executive function and language.	• At T1: no between-group differences; • At T2: no significant differences over time; • No correlation with brain-based measures.
Chen et al., 2018b	Attention, episodic memory, working memory, processing speed, executive function and language.	• At T1: no between-group differences; • At T2: no significant differences over time; • No correlation with brain-based measures.
Conroy et al., 2013a	Verbal memory, visual memory; working memory, processing speed, distractibility and verbal domain.	• At T1: no between-group differences; • At T2: overall improvement, except for the C+ post-menopausal, although no significant between-group differences. • CIA ↑ processing speed correlated with ↑ brain activation from T1 to T2.
Kesler et al., 2017b	Attention, verbal memory, processing speed, executive function, verbal fluency and verbal learning.	• At T1: differences in verbal fluency, verbal memory, attention, processing speed and executive functioning (Kesler et al., 2017b); • At T2: results weren't reported on the paper; • At T3: 59% of C+ had persistent cognitive impairment (CI) while 41% had late onset CI; • 5 brain hub-regions clustering coefficients at T1 predict late onset CI.
Lepage et al., 2014	Visual memory, verbal memory, working memory, and processing speed.	• At T1: no between-group differences; • Overall all domains ↓ at T2 and ↑ at T3 (processing speed was the only "marginally" significant); • At T2: no between-group differences; • ↑ visual memory, working memory and processing speed correlates with ↑ GMV in several frontal areas.
Menning et al., 2017	Attention, visual memory, verbal memory, processing speed, executive function, and motor speed.	• At T1: domain scores and the proportion of cognitively impaired subjects were not significantly different between any of the groups, after controlling for fatigue, perceived stress, anxiety and depression (Menning et al., 2015); • At T2: results weren't reported on the paper; • No significant correlations between brain-measures and neuropsychological tests;
Menning et al., 2018	Attention, visual memory, verbal memory, processing speed, executive function, and motor speed.	• At T1: domain scores and the proportion of cognitively impaired subjects were not significantly different between any of the groups, after controlling for fatigue, perceived stress, anxiety and depression (Menning et al., 2015); • At T2: results weren't reported on the paper; • No significant correlations between brain-measures and neuropsychological tests.
Nudelman et al., 2014	Composite score.	• At T1: no between-group differences; • At T2: no between-group differences ("learning effect" for all groups?); • C+ ↓ composite score correlates with ↑ prefusion change in RPG over time.

C+: women with breast cancer who underwent chemotherapy; C-: women with breast cancer who did not undergo chemotherapy; HC: healthy matched-controls; FA: fractional anisotropy; CI: cognitive impairment; GMV: gray-matter volume; RPG: right precentral gyrus

radial diffusivity (RD), and axial diffusivity (AD) (Deprez et al., 2018).

Baseline results (time point 1) found that two studies had significant between-group differences. McDonald et al. (2013) revealed significant structural changes at baseline by reporting that C- patients had a decrease in gray matter density (GMD) in the left cingulate gyrus compared to healthy controls.

Table 4 Subjective cognitive complaints tools, major results and their correlation with brain-based measures

References	Subjective cognition/measures of cognitive complaints	Major findings
Askren et al., 2014	AFI	• C+ ↑ complaints at T1 predicted ↑ complaints at T2; • C+ ↑ fMRI SV predicts ↑ complaints at T1.
Billiet et al., 2018	CFQ	• C+ ↑ complaints in CFQ distraction, names and word finding from T1 to T2; • ↑ complaints are correlated with ↓ attention and verbal memory, from T1 to T2; • All 3 groups had ↑ complaints at T3 vs T1 for CFQ names, word finding and total score; • C+ complaints at T3 are correlated with fatigue and depression.
Deprez et al., 2014	CFQ	• C+ ↑ complaints from T1 to T2; • C+ ↑ complaints are correlated with ↓ brain activation in multitasking areas at T2.
Jung et al., 2017	AFI	• Similar scores across all groups at each time point; • T3 ↑ complaints are correlated with ↑ worry and ↑ physical symptoms severity, regardless of treatment.
McDonald et al., 2013	BRIEF-A	• C+ ↑ complaints in problem-solving at T2; • C+ ↓ GMD associated with ↑ complaints at T2.
Menning et al., 2017	MOS-Cog	• C+ ↑ complaints associated with ↑ parietal activation.
Menning et al., 2018	MOS-Cog	• C+ ↑ complaints at T2.

C+: women with breast cancer who underwent chemotherapy; C-: women with breast cancer who did not undergo chemotherapy; HC: healthy matched-controls; fMRI: functional magnetic resonance imaging; SV: spatial variance; GMD: gray-matter density; AFI: Attentional Function Index; CFQ: Cognitive Failures Questionnaire; BRIEF-A: Behavioral Rating Inventory of Executive Function; MOS-Cog: Medical Outcomes Study Cognitive Functioning Scale

White matter integrity was also altered in DTI analyzes, since Menning et al. (2018) reported a widespread decrease in FA values in both cancer groups (C+ and C-). However, most studies (71%) reported no between-group differences at this time point.

After chemotherapy (time point 2), VBM studies showed an overall reduction in GMD in C+ patients (Chen et al., 2018a; Chen et al., 2018b; Lepage et al., 2014; McDonald et al., 2010). This reduction was visible in several brain regions such as bilateral frontal (middle and superior frontal gyrus), temporal (left middle temporal gyrus, hippocampus and its adjacent medial structures), and parietal (precuneus) areas. Regarding diffusion tensor models (DTI), C+ patients showed a widespread decrease in FA values affecting several brain regions in frontal, parietal and occipital WM tracts (Billiet et al., 2018). Menning et al. (2018) replicated these findings and found a mild decrease, but only with subsequent ROIs analysis.

At time point 3, nearly one year after chemotherapy, VBM studies revealed a degree of recovery in several brain regions, while the persistent GMD decline was still observed in bilateral frontal (inferior frontal operculum, middle and superior frontal gyrus) and temporal regions (hippocampus and superior and medial temporal gyrus). This pattern was not present in patients who did not receive chemotherapy or in healthy controls (Lepage et al., 2014: McDonald et al., 2010). Regarding DTI, Billiet et al. (2018) found a significant correlation between time after treatment and recovery of WM damage (reflected by increased FA) in two of the four regions analyzed (ROI1: region covering parietal part of corona radiata and corpus callosum and ROI2: region covering frontal part of the superior longitudinal fasciculus). Hence, these results suggest that recovery, previously seen in GMD, is also present in the damage of WM tracts. Also, three to four years after chemotherapy, structural results are similar to baseline levels. At time point 3, the between-group analysis with DTI also confirmed that there were no significant differences across all groups, confirming the hypothesis of recovery previously seen in VBM studies.

Brain Perfusion Outcomes

Nudelman et al. (2014) was the only study that assessed brain perfusion through pulsed arterial spin labeling magnetic resonance perfusion (PASL MRI). This is a noninvasive MRI perfusion technique that provides a marker of regional brain function while quantitatively measuring cerebral blood flow using magnetically labeled arterial blood water as an endogenous contrast tracer (Haller et al., 2016).

Baseline data from this study were congruent with the GMD and WM previous results reporting no between-group differences. One month after chemotherapy, and unlike HC, C+ patients showed increased frontal perfusion in the right precentral gyrus. Table 6 presents all the results from PASL MRI.

Table 5 MRI structural results from baseline (BL/T1) to post-chemotherapy (T2 and T3).

References	Sample	Time-points	Neuroimaging technique	T1	T2	T3
Billiet et al., 2018	25 C+ 14 C- 15 HC	BL; 3-5 M; 3-4Y	DTI (FA)	No between-groups differences.	C+ ↓ FA in corpus callosum, corona radiata, frontal, parietal and occipital WM tracts;	C+ ↑ FA with "time since treatment" in 2/4 ROIS; C+ ↑ WM FA in the 4 ROIs;
Chen et al., 2018a	17 C+ 15 HC	BL; 1 M	VBM	No between-groups differences.	C+ ↓ GMD in the left anterior cingulate gyrus, right insula and left middle temporal gyrus.	N/A
Chen et al., 2018b	16 C+ 14 HC	BL; 1 M	MP-RAGE	No between-groups differences.	C+ ↓ in total GM, total WM and frontal lobe; no significant differences between groups in these reductions.	N/A
Lepage et al., 2014	19 C+ 19 HC	BL; 1 M; 1Y	VBM	Results are reported on Scherling et al. (2012): there were no between-groups differences regarding GM.	C+ ↓ GMD in frontal, temporal, parietal and occipital regions.	C+ persistent ↓ in bilateral frontal (inferior frontal operculum, right middle frontal gyrus) and temporal regions (hippocampus, superior temporal gyrus); C+ ↑ GMD in all other regions decreased at T2 - partial recovery!
McDonald et al., 2010	17 C+ 12 C- 18 HC	BL; 1 M; 1Y	VBM	No between-groups differences.	C+ ↓ GMD in bilateral frontal, temporal (including hippocampus and adjacent medial temporal structures) and cerebellar regions and right thalamus.	C+ showed partial recovery. Areas that showed recovery: bilateral superior frontal, left middle frontal and right superior temporal and cerebellar regions. Areas that showed persistent declined: bilateral cerebellum, right thalamus and medial temporal lobe, left middle frontal gyrus, and right precentral, medial frontal, and superior frontal gyri.
McDonald et al., 2013	27 C+ 28 C- 24 HC	BL; 1 M	VBM	C- ↓ GMD in the left cingulate gyrus.	C+ ↓ GMD in the left middle and superior frontal gyri.	N/A
Menning et al., 2018	26 C+ 23 C- 30 HC	BL; 1 M	DTI (FA & MD)	Results are reported on Menning et al. (2015): ↓ FA in both C+ and C-, indicating lower WM integrity.	Voxel-analysis showed no differences; ROIs analysis revealed modest declines C+ ↓ WM FA in the right SLF and ↑ MD in the right CST. C- ↓ WM FA corpus collosum and ↓ WM MD in the genu.	N/A

C+: women with breast cancer who underwent chemotherapy; C-: women with breast cancer who did not undergo chemotherapy; HC: healthy matched-controls; DTI: diffusion tensor imaging; FA: fractional anisotropy; MD: mean diffusivity; MP-RAGE: magnetization prepared rapid gradient echo; VBM: voxel-based morphometry; GM: gray-matter, GMD; gray-matter density; WM: white-matter; SLF: superior longitudinal fasciculus; CST: Corticospinal tract; ROIs: regions of interest; N/A: not applicable

Table 6 PASL MRI results from baseline (BL/T1) to post-chemotherapy (T2)

References	Sample	Time-points	Neuroimaging technique	T1	T2	T3
Nudelman et al., 2014	27 C+ 26 C- 26 HC	BL; 1 M	PASL MRI	No between-groups differences.	C+ ↑ perfusion in the right precentral gyrus (not associated with ↓ frontal GMD).	N/A

C+: women with breast cancer who underwent chemotherapy; C-: women with breast cancer who did not undergo chemotherapy; HC: healthy matched-controls; PASL MRI: pulsed arterial spin labeling magnetic resonance perfusion; GMD: gray-matter density; N/A: not applicable

Brain Activity Outcomes

Studies that assessed brain activity (n = 8) (Askren et al., 2014; Conroy et al., 2013a; Deprez et al., 2014; Jung et al., 2017; Kesler et al., 2017b; McDonald et al., 2012; Menning et al., 2017; Zunini et al., 2013) applied functional neuroimaging (fMRI), a procedure that measures brain activity during rest (resting state or rs-fMRI) or during a cognitive task. With this procedure, changes are measured in regional cerebral blood flow based on the levels of activity of the blood oxygenation level-dependent signal (BOLD) (van der Werff, van den Berg, Pannekoek, Elzinga, & van der Wee, 2013). Verbal working memory (n = 4), verbal recall (n = 1), visual and auditory multitasking (n = 1), executive function and memory (n = 1) were the cognitive domains assessed through specific neuroimaging tasks. Regarding task performance, three studies reported a trend towards less accuracy, more errors or worse reaction time for C+ patients, before and after chemotherapy (Askren et al., 2014; Jung et al., 2017; McDonald et al., 2012). Most studies applied imaging, contrast-based comparisons for different tasks for each patient and for each time point assessed (Askren et al., 2014; Conroy et al., 2013a; Deprez et al., 2014; Jung et al., 2017; McDonald et al., 2012; Menning et al., 2017; and Zunini et al., 2013). Table 7 presents the cognitive domains, related-tasks and fMRI major results.

Baseline data (time point 1) revealed that 75% of these studies showed indicators of compromised function. Abnormalities were found in tasks related to verbal working memory (Askren et al., 2014; McDonald et al., 2012), executive functioning (Menning et al., 2017), and verbal recall (Zunini et al., 2013). McDonald et al. (2012) and Menning et al. (2017) revealed similar patterns of frontal and parietal hyperactivation in both cancer groups (C+ and C) in executive functioning and verbal working memory tasks, while Zunini et al. (2013) found a decreased activation in the anterior cingulate cortex in the C+ group (vs HC) in a verbal recall task. Additionally, Askren et al. (2014) found that C+ patients presented higher spatial variance as a signal of neural inefficiency in the executive network, which covers the same brain areas previously reported for verbal working memory. Jung et al.' (2017) revealed a similar trend in their results. Lastly, Kesler and colleagues (Kesler et al., 2017b) reported that both cancer groups (C+ and C-) showed significantly altered local connectivity in several frontal (right middle inferior orbital frontal gyrus and right medial superior frontal gyrus) and parietal (right inferior parietal lobe) areas. Conroy et al. (Conroy et al., 2013a), Deprez et al. (2014) and Jung et al. (2017) also reported no between-group differences in brain activation in tasks related to verbal working memory and multitasking, at baseline data.

After chemotherapy (time point 2), three studies (Askren et al., 2014; Jung et al., 2017; Kesler et al., 2017b) reported the results of prediction models for post-chemotherapy cognitive impairment. The remaining studies reported between-group differences in brain activation ($n = 2$) and deactivation ($n = 3$). Regarding hyperactivation, Conroy and colleagues (Conroy et al., 2013a) demonstrated that the pattern of change in brain activity from pre to post-treatment varies according to the patients' pre-treatment menopausal status, by revealing that patients with chemotherapy-induced amenorrhea (CIA) had increased brain activity in a working memory task. The same pattern of increased parietal activation was found by Menning et al. (2017) in an executive functioning task. This hyperactivation was accompanied by worse physical functioning, higher fatigue and higher cognitive complaints.

Studies reporting brain deactivation after chemotherapy revealed decreased brain activity in parietal, frontal and temporal areas in tasks related to multitasking, working memory and verbal recall (Deprez et al., 2014; McDonald et al., 2012; Zunini et al., 2013). In McDonald et al. (2012) both cancer patient groups (C+ and C-) had decreased frontal activation. There were no regions where HC showed decreased activation from baseline to time point 2.

Three papers focused on a third time point assessment such as Kesler and colleagues (2017b) who focused on determining if baseline rs-fMRI could accurately predict long-term cognitive outcomes in C+ patients. This study examined three different predictive models. The final model retained five brain regions (left lingual gyrus, left calcarine, right insula, right middle temporal gyrus and right olfactory area) categorized as "hubs" (i.e. globally connected regions). Jung et al. (2017) revealed that C+ patients experienced cognitive problems, seven months after chemotherapy, since their deficit score in the VWMT did not change over time, while HC scores improved coinciding with a learning effect. Also consistent with

Table 7 Functional MRI results from baseline (BL/T1) to post-chemotherapy (T2 and T3)

References	Sample	Time-points	Domain	Neuroimaging task	T1/BL results	T2 results	T3 results
Askren et al., 2014	28 C+ 37 C- 32 HC	BL; 1 M	Verbal Working-memory	VWMT	C+ (vs C-): ↑ SV in the EN (anterior cingulate, left frontal, right frontal, left parietal, and right parietal). T1 levels of SV in the EN predict post-treatment fatigue severity and cognitive complaints.	C+ ↑ fatigue; C+ gave more errors on the VWMT task than the other two groups combined.	N/A
Conroy et al., 2013a	9 pre (CIA) and 9 post-menopausal C+ 6 pre and 6 post-menopausal HC	BL; 1 M	Working-memory	N-Back	No between-groups differences.	CIA ↑ magnitude activation; other groups maintain similar levels over time.	N/A
Deprez et al., 2014	18 C+ 16 C- 17 HC	BL; 4-6 M	Multitasking	Visual and Auditory task	No between-groups differences.	C+ ↓ brain activity in the left anterior cingulate gyrus and in the intraparietal sulcus.	N/A
Jung et al., 2017	28 C+ 34 C- 30 HC	BL; 5 M; 1Y	Verbal Working-memory	VWMT	C+ ↑ SV in EN (but ns).	Not reported.	C+ ↓ performance of the task and ↑ SV in the EN.
Kesler et al. 2017b	31 C+ 43 HC	BL; 5 M; 1Y	N/A	Rs-fMRI	Results reported elsewhere with same of the patients from the current sample (Kesler et al., 2017): C+ showed altered local connectivity in several frontal (right middle inferior orbital frontal gyrus and right medial superior frontal gyrus) and parietal (right inferior parietal lobe) areas.	Not reported.	55% of C+ have CI at T3; CI at T3 is predicted by T1 activation levels in five brain regions (left lingual gyrus, left calcarine, right insula, right middle temporal gyrus and right olfactory area) but no patient/medical features.
McDonald et al., 2012	16 C+ 12 C- 15 HC	BL; 1 M; 1Y	Working-memory	N-Back	C+ and C- (vs HC): ↑ bifrontal and ↑ right parietal activation.	C+ and C- ↓ left frontal hyperativation and ↓ middle frontal gyrus activation.	C+ again with ↑ left frontal activation; C+ and C- ↓ middle frontal gyrus activation.
Menning et al., 2017	28 C+ 24 C- 31 HC	BL; 6 M	Memory and executive functioning	ToL & Paired Associates Memory task	C+ and C- (vs HC): ↑ prefrontal hyperactivation.	C+ ↑ parietal activation (IPC, precunneus and SPC).	N/A
Zunini et al., 2013	21 C+ 21 HC	BL; 1 M	Verbal Recall	Verbal Recall Task	C+ ↓ activation on the anterior cingulate cortex (after controlling for anxiety and fatigue).	C+ ↓ activation in the bilateral insula, the left inferior orbitofrontal cortex and the left middle temporal gyrus.	N/A

C+: women with breast cancer who underwent chemotherapy; C-: women with breast cancer who did not undergo chemotherapy; HC: healthy matched-controls; VWMT: verbal working-memory task; SV: spatial variance; EN: executive network; CIA: chemotherapy-induced amenorrhea; rs-fMRI: resting-state functional magnetic resonance imaging; CI: cognitive impairment; ToL: Tower of London; IPC: inferior parietal cortex; SPC: superior parietal cortex; N/A: not applicable

these task performance results, C+ patients showed greater neural inefficiency (indexed by greater spatial variance) in the executive network. McDonald et al. (2012) also observed different patterns of brain activation at this time point. For the C+ group, results revealed a working memory frontal hyperactivation that returned to baseline levels at time point 3.

Discussion

Several studies focused on fundamental questions about CRCI and contributed to its recent inclusion in the National Comprehensive Cancer Network Survivorship Guidelines (Delinger et al., 2016). However, important questions remain unanswered about risk factors, time course, other treatment implications, and the neurobiological mechanisms involved. This systematic review explored the neurobiological mechanisms underlying the course of CRCI in breast cancer patients.

Is There Evidence for Objective and Subjective CRCI?

When analyzing cognitive function, it is recommended the distinction between objective cognitive function, measured by standardized neuropsychological tests, and subjective cognitive function, measured through the amount of cognitive problems perceived by patients (Pullens, De Vries, & Roukema, 2010).

When examining pre-treatment performance across multiple cognitive domains, data from this review suggested that breast cancer patients (C+ and C-) do not differ significantly from healthy controls since only one study (Kesler et al., 2017b) reported between-group differences. This evidence contradicted previous studies supporting the existence of cognitive deficits before adjuvant treatment in about 20 to 40% of breast cancer patients (Ahles et al. 2018; Lange et al., 2014). In addition, neuroimaging studies generally have far fewer participants than studies using only neuropsychological tests. Therefore, most neuroimaging studies have small samples that often result in statistically underpowered studies (Cremers, Wager, & Yarkoni, 2017).

However, Kesler and colleagues (2017b) suggested that some patients presented cognitive impairment even before breast surgery in domains such as processing speed and verbal fluency. These results have also been congruently found in other studies (Ando-Tanabe et al., 2012) raising the question about the importance of including a new baseline measure before surgery with general anesthesia, in order to isolate its implications on cognition and better comprehend risk factors for CRCI.

Nevertheless, the findings of the present review are consistent with other studies that did not reveal baseline differences in patients' neuropsychological performance (Cerulla et al., 2017; Debess, Riis, Pedersen, & Ewertz, 2009; Klemp et al., 2018).

Shortly after chemotherapy, most longitudinal studies included in this review (83%) suggested that chemotherapy was not associated with cognitive side effects which contradicts most cross-sectional studies that support deficits associated with cytotoxic treatment (Frank, Vance, Triebel, & Meneses, 2015). One study even reported a general improvement in all cognitive domains immediately after chemotherapy except in the post-menopausal group. This result seems to indicate that the pattern of change in cognition from pre to post-treatment in C+ patients may vary according to their baseline menopausal status (Conroy et al., 2013a).

In a long-term post-chemotherapy assessment (one to four years after treatment), the present review suggested that there appears to be a general improvement in verbal memory and processing speed (Lepage et al., 2014; Billiet et al., 2018). In contrast, cross-sectional studies performed up to three years after treatment showed delayed cognitive dysfunction in most patients (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Castellon et al., 2004). These findings may reflect different study designs, as previous longitudinal studies also revealed that some breast cancer patients improved after chemotherapy (Ando-Tanabe et al., 2012; Bender et al., 2006; Conroy et al., 2013a), while cross-sectional studies are unable to follow this pattern of recovery. However, some longitudinal studies also confirmed that a significant percentage of patients still showed cognitive deficits one year after treatment (Collins, Mackenzie, Tasca, Scherling, & Smith, 2012; Quesnel et al., 2009; Wefel et al., 2010). It is important to note that longitudinal studies reported a significant percentage of patients with baseline cognitive deficits, which did not occur in the studies covered in the present review suggesting that baseline neuropsychological status may influence performance over time and, therefore, it is crucial to evaluate these patients prior to treatment to better understand the evolution of CRCI over time (Lange et al., 2014).

The comparison between these studies was difficult, mainly hurdled by the variability of neuropsychological tools applied to evaluate the same cognitive aspects, which resulted in the application of 20 different measures to evaluate nine cognitive domains (see Table 2). Therefore, the criteria for the classification of impairment differed between studies since different tests presented different reference data and performance cutoff points while measuring the same cognitive domain.

In an attempt to address the assessment of cognitive function, the International Cognition and Cancer Task Force (ICCTF) published a series of guidelines to consider when applying neurocognitive tools to assess CRCI. Recommended tests (HVLT-R, TMT and COWA) were chosen based on their psychometric qualities and results across studies (Wefel et al., 2011). In the present review, studies that reported significant differences applied some of these instruments (Lepage et al., 2014; Kesler et al., 2017b), which are in line with these recommendations.

The present review also supports that mild cognitive impairment after chemotherapy is more commonly reported by patients than objectively measured by neuropsychological tests (Boykoff, Moieni, & Subramanian, 2009). Immediately following systemic treatment, most studies reported subjective altered cognition (71%), especially regarding problem-solving and distraction (Deprez et al., 2012; Billiet et al., 2018; McDonald et al., 2013), that could not support objective confirmation by neuropsychological test results. This lack of association between objective and subjective cognition in cancer patients raises important questions regarding the sensitivity and ecological validity of the existing neuropsychological tools for the assessment of the CRCI (Klemp et al., 2018; Spooner & Pachana, 2006).

However, increasing evidence confirms that neuropsychological impairment and self-perceived cognitive dysfunction are independent phenomena in cancer patients (Hermelink et al., 2010). The associations found in the present review between post-treatment subjective complaints and psychological factors such as fatigue, depression, worry as well as the severity of self-reported physical symptoms, are in accordance with this perspective. Several studies have reported similar results, suggesting that breast cancer patients negatively judge their cognitive performance if they exhibit negative emotional functioning (Biglia, Torta, Sismondi, & Torta, 2011; Cimprich, So, Ronis, & Trask, 2005; Ganz et al., 2013; Von Ah & Tallman, 2015).

Although not easily recognized with neuropsychological tests – the golden standard of CRCI research – perceived cognitive impairment is present and may strongly affect patients' perceptions of quality of life (Ando-Tanabe et al., 2012; Shilling & Jenkins, 2007). Neuroimaging may help soften these controversies as it has the potential to be more sensitive to mild cognitive impairment in this population than neuropsychological testing (Deprez et al., 2014; Simó, Rifà-ros, Rodriguez-Fornells, & Bruna, 2013).

Does Cancer Affect the Brain before Treatment Initiation?

The present review suggested that breast cancer patients did not exhibit gray matter perfusion and structural changes prior to chemotherapy, as the only baseline gray matter difference was found in a single cluster in the left cingulate gyrus in which C- patients showed lower gray matter density than controls. This finding is unlikely to be related to cancer itself as no differences were observed between groups in the C + group, as pointed out by the authors (McDonald et al., 2013).

Results differed regarding WM with one study presenting lower WM integrity in both patient groups (C+ and C-), compared to healthy controls (Menning et al., 2018). The other DTI study from this review (Billiet et al., 2018) failed to replicate these differences while controlling for depression. However, it is also important to note that Menning's sample was six years older than Billiet's, and also 41% of their C+ patients were on menopause (vs all pre-menopausal women from Billiet's study). These results seem to suggest that age and menopausal status before treatment initiation may underlie these structural white matter abnormalities and explain these different results, although further research is warranted.

Regarding cerebral perfusion, the present review suggests that the results of the MRI technique followed the structural findings, showing no changes in arterial labeling perfusion. Although the MRI technique has already proved its applicability in longitudinal studies of cerebral perfusion in healthy individuals and patients with other conditions (Haller et al., 2016), Nudelman's study was the first to evaluate brain perfusion in cancer samples and, therefore, comparisons are limited.

Regarding brain function, pre-chemotherapy patients showed a trend towards more errors on cognitive tasks compared to C- and HC (Askren et al., 2014). Functional neuroimaging studies also appear to be more consistent in reporting functional changes, at baseline. The present review found a predominant pattern of baseline frontal and parietal hyperactivation and lower task performance in patients (vs HC) in working memory, executive functioning and verbal recall tasks. These findings are consistent with other cross-sectional studies that focused on functional changes before treatment, and confirmed this review's findings of frontal hyperactivation while performing working memory-related tasks (Cimprich et al., 2010; McDonald et al., 2012; Scherling et al., 2011; Scherling, Collins, MacKenzie, Bielajew, & Smith, 2012a).

Several psychological and biological mechanisms have been proposed to justify functional impairments (Cimprich et al., 2010) and the present review emphasizes the potential confounding role of the number of days since surgery and fatigue in brain activity before chemotherapy. In fact, regarding days since surgery (Zunini et al., 2013), one possible explanation may have to do with the side effect of general anesthesia (Scherling, Collins, MacKenzie, Bielajew, & Smith, 2012b), accompanied by surgical stress and its influence on inflammatory responses (Schneemilch & Schilling, 2004). However, an important limitation of most pre-chemotherapy studies was the lack of a pre-surgical evaluation to confirm this theory. Only one study assessed patients before any cancer treatment, including surgery with general anesthesia (Kesler et al., 2017b), showing significant impairment such as lower function in frontal, parietal and temporal networks on a rs-fMRI. Interestingly, these findings were unrelated to psychological distress suggesting, therefore, a direct effect of cancer on the brain through mechanisms such as neuroinflammation (Kesler et al., 2017a).

A second explanation for baseline CRCI in this review were the elevated levels of fatigue and its association with greater neural inefficiency measured by higher spatial

variance in the executive network (Askren et al., 2014). Several studies had already confirmed the detrimental effects of fatigue on working memory in women recently diagnosed with breast cancer (Cimprich et al., 2005; Ehlers et al., 2017). Additionally, this finding is congruent with other studies suggesting that fatigue is highly prevalent in patient samples (Morrow, 2007) and is an important predictor of the baseline CRCI in cancer patients scheduled for treatment (Churchill et al., 2015; Menning et al., 2015). Cancer-related fatigue has also been associated with higher levels of proinflammatory cytokines (Raudonis, Kelley, Rowe, & Ellis, 2017), frequently proposed as a possible mechanism underlying CRCI (Jenkins et al., 2016), although requiring further investigation.

In summary, pre-treatment cognitive impairment is now widely accepted among researchers and clinicians being crucial to define CRCI (Lange et al., 2014). The functional results of neuroimaging raised important questions about the independent impact of chemotherapy on cognition, showing the need for pre-treatment assessments and a better understanding of the neurobiological and psychological factors underlying CRCI.

In addition, an important finding of the present review was the frontal and parietal brain hyperactivation found in breast cancer patients, although no structural or cerebral perfusion changes were found in the gray matter. These results also seem to suggest that functional magnetic resonance imaging may be more sensitive in detecting CRCI changes at this early stage of the disease in breast cancer patients.

Does Chemotherapy Affect Breast Cancer Patients' Brains?

Overall, the present review suggests that a pattern of brain structural, perfusion, and functional changes may be found in breast cancer patients after chemotherapy (up to six months).

Most neuroimaging studies were conducted with breast cancer survivors evaluated years after treatment. The present review allows to better understand the immediate effects of chemotherapy on patients' brain, suggesting that VBM showed an overall decrease in GMD frontal, temporal and parietal areas. The left middle temporal gyrus, left insular cortex, left anterior cingulate gyrus (Chen et al., 2018a; Lepage et al., 2014), right hippocampus (Lepage et al., 2014; McDonald et al., 2010), right middle frontal gyrus (Lepage et al., 2014; McDonald et al., 2013), and right precuneus (Lepage et al., 2014) were the brain regions most commonly affected.

Lepage et al. (2014) was the only study to find a significant positive correlation between neuropsychological testing (working memory, verbal recall and processing speed) and gray matter volume (GMV) in several frontal areas. Therefore, the results of the present review are consistent with the results of previous cross-sectional studies that showed distributed gray matter changes in breast cancer patients shortly after chemotherapy, with little or no correlation with neuropsychological tests. For example, Inagaki and colleagues (2007) performed a longitudinal assessment with a 1-year and 3-year evaluation after cancer surgery. In the 1-year study, the results revealed the same pattern as this review since C+ patients had smaller gray and white matter volumes in areas including prefrontal, parahippocampus, cingulate gyrus and precuneus suggesting these areas are the most commonly affected by chemotherapy soon after the treatment ends.

In the present review, WM abnormalities were measured with diffusion tensor analysis (DTI) that also revealed decreased FA values (a measure of WM coherence and organization) in frontal and occipital areas of the brain (Billiet et al., 2018), although the results with this technique were more modest and require additional analyses (Menning et al., 2018). Billiet et al. (2018) reported a widespread decline in WM integrity while controlling for depression scores (Deprez et al., 2012) finding also a significant correlation between neuropsychological test results on attention and working memory with WM frontal and occipital abnormalities. Similar results were found in a prior cross-sectional study from the same group (Deprez et al., 2011). Nevertheless, Menning et al. (2018) could not replicate these findings since whole-brain analysis did not reach significance. However, when performing further ROIs analysis, C+ patients revealed a larger decline in WM tracts in the right superior longitudinal fasciculus (SLF) and in the corticospinal tract suggesting that DTI's ROIs analysis were more sensitive to WM damage, in these patients.

Additionally, interesting similarities can be found between longitudinal VBM and DTI structural changes in the brain, such as its diffuse patterns, lobes affected and few correlations with neuropsychological testing. The present review seems to suggest that test results for working memory showed more correlations with structural changes in frontal GMV (Lepage et al., 2014) and frontal WM integrity (Billiet et al., 2018; Deprez et al., 2012) acutely after chemotherapy. The gray and white matter alterations were not present in control groups assessed at matched intervals, raising the hypothesis that these effects may be due to chemotherapy treatment and its cytotoxic agents rather than reflecting solely host factors or other treatment effects (McDonald et al., 2013). Research performed with animal models reported similar results, suggesting that several chemotherapeutic agents may have adverse effects on information acquisition, learning and memory and, despite some recovery, impairment can be long lasting (Janelsins et al., 2017).

The literature has shown several mechanisms that may explain brain's structural changes. It is already known that other factors besides demyelination and edema, such as neuroinflammation, play an important role in MRI signal changes

(Assaf & Pasternak, 2008). Pro-inflammatory cytokines, such as IL-1, IL-6 and TNFα, have previously been suggested to play an important role in CRCI (Jenkins et al., 2016; Kesler et al., 2013). A relationship between cytokine levels and regional brain volumes has been previously reported in breast cancer patients. Kesler et al. (2013) found that breast cancer survivors' left hippocampal reduced volume were significantly correlated with elevated concentration of IL-6 and TNF-α. These same pro-inflammatory cytokines have also been suggested to influence DTI measures of WM integrity (Briones & Wood, 2014).

Regarding perfusion, Nudelman et al. (2014) reported a frontal hyperperfusion in the right precentral gyrus in C+ patients. Interestingly, the frontal hyperfusion did not correlate with the frontal decreased GMD and that may corroborate the sensitivity of this technique to measure mild cognitive impairment previously reported under other conditions, such as mild dementia (Alexopoulos et al., 2012; Haller et al., 2016), indicating its potential as an alternative to other techniques.

Results regarding functional MRI, C+ women made more errors in cognitive tasks than women from C- and HC combined (Askren et al., 2014; Jung et al., 2017; McDonald et al., 2012) suggesting a mixed pattern oscillating between brain activation and deactivation after chemotherapy when compared to controls in several frontal, parietal and temporal areas. Three longitudinal fMRI studies (Deprez et al., 2014; McDonald et al., 2012; Zunini et al., 2013) reported frontoparietal hypoactivation in multitasking, working memory, and verbal recall tasks, while two studies (Conroy et al., 2013a; Menning et al., 2017) reported hyperactivation after chemotherapy and during working memory and executive functioning tasks.

The hyperactivation is congruent with previous cross-sectional studies on memory tasks performed by survivors, suggesting a functional compensatory process to maintain adequate levels of performance during these tasks (Ferguson, McDonald, Saykin, & Ahles, 2007; Silverman et al., 2007). In line with these findings, Silverman et al. (2007) assessed breast cancer survivors 5–10 years after chemotherapy with a verbal recall task and found that specific regions of frontal cortex, cerebellum, and basal ganglia were significantly activated in individuals treated with chemotherapy compared to controls who had never received this treatment. Also, Kesler, Kent, and O'Hara (2011) evaluated 25 C+ women and 19 C- women and results revealed a significant hypoactivation in the left middle dorsolateral prefrontal cortex and in the premotor cortex compared to controls.

The mixed fMRI pattern of activation/deactivation results could be related to specific task performance. Hypoactivation was found in tasks related to multitasking (Deprez et al., 2014) and verbal recall (Zunini et al., 2013), while hyperactivation was found in executive functioning (Menning et al., 2017), suggesting that the effects of systemic treatment are different depending on the domain targeted by a specific task. Nevertheless, Conroy et al. (2013a) and McDonald et al. (2012) found different activation patterns while applying the same verbal working memory task (N-back). However, the latter two studies had important differences in their patients' characteristics, since Conroy's sample is seven years younger than McDonald's, and age has previously been shown to be an important confounding factor for CRCI (Ahles et al., 2018; Chen et al., 2018a; Chen et al., 2018b; Kesler et al., 2011). Also, patients in the Conroy's study who exhibit the highest levels of brain activation were pre-menopausal at baseline, whereas in the McDonald's sample most patients were already in menopause before chemotherapy. Therefore, the present review also suggests that the neural stress of chemotherapy-induced amenorrhea and the abrupt decrease in estrogen caused by chemotherapy could be associated with a compensatory hyperactivation to maintain cognitive function in verbal working memory tasks (Conroy et al., 2013a). Changes in hormone levels, such as estrogen in breast cancer samples, were previously associated with cognitive decline (Castellon et al., 2004; Schilder et al., 2010). These results highlight the need for further investigation on the interaction between cognitive aging, menopausal status and hormone therapy.

Signs of compromised frontoparietal networks were also related to the patient's complaints in two studies regarding multitasking and executive functioning tasks (Deprez et al., 2014; Menning et al., 2017). The correlation between brain activity and cognitive complaints after chemotherapy has been previously described in prior retrospective studies (Ferguson, McDonald, Saykin, & Ahles, 2007; Kesler et al., 2011), suggesting the existence of neurobiological mechanisms underlying perceived change in cognitive functioning (Askren et al., 2014; Deprez et al., 2014).

Interestingly, the present review also suggests an overlapping of brain regions affected and commonly reported in both structural and functional MRI studies. This overlap has been previously reported by other authors (Ruiter et al., 2011; Kesler et al. Kesler et al., 2017a). In this review, brain regions such as the left anterior cingulate, middle frontal gyrus, precuneus, bilateral insula and left middle frontal gyrus have been structurally and functionally acutely affected after chemotherapy. Such conclusion suggests the importance of CRCI neuromarkers, although more research is required.

Is There Recovery after Chemotherapy Brain-Damage?

The present review confirmed an optimistic theory towards partial recovery after chemotherapy-related damage since both structural and functional MRI studies converged into a normalization pattern on the longer follow-up assessments, even when the majority of patients (70.9%) were still on hormonal therapy.

One year after chemotherapy, structural recoveries in the GMD appeared to be partial, as some areas recovered fully to baseline levels, while other regions experienced persistent decline. These regions were bilaterally distributed in frontal (inferior frontal operculum, middle and superior frontal gyrus) and temporal areas (hippocampus and superior and medial temporal gyrus) (Lepage et al., 2014; McDonald et al., 2010). The partial recovery is congruent with prior neuroimaging studies. Conroy et al. (2013b) found a positive correlation between post-chemotherapy interval (PCI) and GMD in frontal regions. Inagaki et al. (2007) also assessed breast cancer survivors at 1-year and 3-years after cancer surgery. Comparisons of gray and white matter volumes (vs HC) revealed that, as previously described, patients had smaller gray matter and white matter, including prefrontal, parahippocampal, cingulate gyrus, and precuneus in the 1-year study. However, over time recovery was found, since no differences between groups (C+ and HC) were observed in the 3-year study. Nevertheless, other neuroimaging studies with breast cancer survivors revealed long-term persistent hippocampal atrophy (Bergouignan et al., 2011; Apple et al., 2017; Kesler et al., 2013). It is still unclear which patients will suffer a persistent reduction in hippocampal volume and further investigation is needed. A possible explanatory mechanism for these long-term brain abnormalities may be the patient's genetic status. Previous studies revealed an association between Alzheimer's disease, cognitive decline and the apolipoprotein E epsilon 4 allele (APOE epsilon 4). APOE status may be a key element for neurodegeneration and a potential genetic biomarker for increased vulnerability to CRCI (Ahles et al., 2003). Further prospective studies combining APOE status with neuroimaging results are needed to examine the interactions between aging, genetic risk and cancer-related cognitive impairment.

Regarding WM integrity, in the present review, Billiet et al. (2018) also revealed a longitudinal recovery reflected by increased FA values (a measure of coherence and organization) 3–4 years after treatment. These results are corroborated by improved neuropsychological performance in working memory and processing speed tasks, seen in both DTI and VBM studies (Billiet et al., 2018; Lepage et al., 2014). Interestingly, Koppelmann's study (2012a) found that 21 years after chemotherapy, gray matter volume was still damaged. However, no significant differences were observed in the white matter. Nevertheless, different results regarding diffusion tensor analysis have been suggested in prior studies (Abraham et al., 2008; Kesler, Watson, & Blayney, 2015; Stouten-Kemperman et al., 2015). Abraham et al. (2008) also reported different results from Billiet's study by assessing a sample of 10 patients (vs HC) reporting cognitive complaints two years after chemotherapy. This study demonstrated decreased integrity of the genu of the corpus collosum using FA values. Billiet's patients also revealed higher cognitive complaints at time point 3, which did not correlate with improved FA values. These differences did not seem to be attributed to the patient's characteristics such as age and menopausal status (similar between these two studies), but might reflect the importance of the post-chemotherapy interval and potential recovery over time, since Abraham's sample was assessed two years after chemotherapy and Billiet's assessment was performed 3–4 years later.

Kesler et al. (2015) also assessed 34 breast cancer survivors six years after chemotherapy and also applied DTI analysis. Results revealed that, compared to healthy controls, the breast cancer group demonstrated significantly lower FA values and significant cognitive impairment. It is important to note that this study has an important limitation regarding the variability of post-chemotherapy intervals across patients (from five months up to 14 years after treatment) that may not have been able to capture the two-phase process of initial diffuse chemotherapy-induced white matter injury followed by its recovery (Billiet et al., 2018).

Considering the results, the present review also seems to suggest that gray matter differences assessed with VBM were more sensitive to early recovery of CRCI brain damage and more resistant to study characteristics, since results were more consistent over time regarding recovery. It is important to emphasize that DTI studies were fewer with smaller sample sizes than VBM.

Regarding functional MRI, the results seem to present a more modest recovery. Jung et al. (2017) reported that women treated with chemotherapy showed a persistent deficit in cognitive task performance (verbal recall), seven months post-chemotherapy, while healthy controls displayed continuous improvement over the same period. Jung's third time point assessment is equivalent to the post-chemotherapy interval found in other fMRI studies for the second assessment (e.g. Deprez et al., 2014, second follow-up 4–6 months after chemotherapy), and, therefore, might not be able to capture recovery. Kesler and colleagues (2017b) also reported that 55% of the sample had CRCI (one year after treatment ends), which is also congruent with the hypothesis of partial recovery since the rest of the sample did not reveal cognitive impairment. While the results from Kesler and colleagues' may be consistent with the recovery hypothesis, they are also consistent with the idea that only a subset of patients experiences CRCI, i.e., while some patients may have not recovered over time, it is also possible that some of them were never impaired.

McDonald et al. (2012) found working memory frontal hyperactivation with an interesting trajectory over time that was present at baseline, decreased acutely after chemotherapy and recovered (partially) to meet baseline compensatory hyperactivation levels. Although some frontal areas gave no signs of recovery by a continuous activation decrease over time, these results confirmed an optimistic theory that chemotherapy-related brain damage can become less

prominent with time. When examining the relationship between frontal activation changes and GMD previously reported by McDonald's group (2010), both studies are in line when showing that the left inferior frontal gyrus shows the same pattern of decreased GMD/working memory activation from baseline to acutely after chemotherapy, with return to baseline GMD/activation one year later.

Similar results were found in a later longitudinal study that are in accordance with the partial recovery theory. Dumas et al. (2013) assessed nine breast cancer patients longitudinally in attention and executive function tasks, but without a control group for comparison (hence, excluded from this review). Results showed decreased functional connectivity one month after chemotherapy that partially returned to baseline levels one year later in the dorsal anterior attention network. Decreased connectivity was seen in the default mode network at one month and one year following chemotherapy in the posterior cingulate cortex. Interestingly, and as previously reported, this study also found increased subjective memory complaints one year later, suggesting that the injurious effect of chemotherapy on brain functional connectivity could be related to self-reported cognitive complaints (Abraham et al., 2008; Dumas et al., 2013).

Several studies with breast cancer survivors also showed hypoactivation in executive functioning tasks (Ruiter et al., 2011; Kesler et al., 2011; Miao et al., 2016; Tao et al., 2017). It is also important to note that these different findings could reflect different neuroplasticity recovery patterns associated with the task and region specificity since working memory tasks revealed improvement over time while executive functioning did not. Nevertheless, the reported studies had a cross-sectional design and, therefore, they might not be able to see over time recovery (Dumas et al., 2013; McDonald et al., 2012).

In conclusion, the present review suggested improved brain function over time, although this recovery is neither total nor encompassing all the cognitive domains and brain regions initially affected. Also, it is still unclear which patients will endure persistent brain structural and functional abnormalities and which patients will be impaired or recover over time, and more research is required. Some deficits seem to remain over time in a subset of patients (up to 21 years after chemotherapy, see Koppelmans et al., 2012b), which is also congruent with studies reporting higher levels of cognitive complaints at longer follow-up assessments (Abraham et al., 2008; Billiet et al., 2018; Dumas et al., 2013; Janelsins et al., 2017; van Dyk et al., 2017).

Clinical Implications

Since chemotherapy will still be the gold standard for cancer treatment in the coming years, it is critical that we understand its impact on the central nervous system and then use this knowledge to develop new prevention and recovery strategies. Recent randomized controlled trials confirmed the important contribution of cognitive training programs for the improvement of attention, memory, processing speed and executive functioning in cancer survivors (Treanor et al., 2016). Other interventions have been the target of increasing research, but their effectiveness has not been established. A recent review (Von Ah & Jansen, 2014), confirmed that cognitive-behavioral therapy (CBT) significantly improved objective and subjective cognition in some patients, although more research is needed. Mindfulness programs have also been suggested to enhance working memory and executive functioning in non-cancer participants (Chiesa, Calati, & Serretti, 2011). Hence, further research is needed to establish the efficacy of CBT and mindfulness for the treatment of CRCI. Furthermore, the randomized controlled trials focusing on intervention strategies, could also implement and benefit from the contribution of neuroimaging techniques for a more rigorous evaluation of cognitive difficulties in these patients. While focusing on treatment efficacy assessed through MRI, promising results can already be found in recent neuroimaging studies about the potential benefits of physical exercise for cancers survivor's quality of life and cognitive functioning (Campbell et al., 2018; Gentry et al., 2018).

Conclusion

This review found no evidence for neuropsychological, gray matter structural and perfusion changes before chemotherapy treatment. Functional changes were evident and demonstrated a frontoparietal hyperactivation during working memory tasks, suggestive of higher fMRI sensitivity to detect lower task performance and cognitive impairment at this early stage of the disease process. Fatigue and number of days since surgery were the two confounding factors proposed to mediate these findings, suggesting a direct effect of cancer on the brain via mechanisms such as neuroinflammation (Kesler et al., 2017a). Acutely, after chemotherapy, the present review suggested that a pattern of frontal structural, perfusion and functional changes could be found in a subset of breast cancer patients.

Working memory was the most predominant cognitive domain across studies, showing correlations with structural changes in frontal GMV (Lepage et al., 2014) and WM integrity (Billiet et al., 2018; Deprez et al., 2012). Findings of frontal hyper and hypo-activity seem to be dependent on age, menopausal status at baseline and domain targeted by a specific fMRI task, although requiring further investigation.

Years after chemotherapy, the present review showed evidence of a partial neuropsychological, structural, and functional recovery. This evidence was already present in GMD and VBM studies one year after chemotherapy ended. Depending on the post-chemotherapy interval, some regions (such as inferior frontal regions and hippocampus) remained

affected chronically by adjuvant treatments, suggesting that some abnormalities might still persist over time and never entirely normalize.

This review found converging evidence from structural and functional studies that show a particular vulnerability of frontal lobes to CRCI, known to be critical for working memory (Wefel & Schagen, 2012). Possible CRCI neuromarkers were also discussed. Since working memory is the most reportedly affected cognitive domain in these studies, the present review can also point to a specific vulnerability of working memory due to chemotherapy treatment and a later improvement. However, most of the included studies focused on the consequences of chemotherapy for patients' working memory and, therefore, future research with magnetic resonance imaging should focus on other cognitive domains such as learning ability, executive function, attention, decision-making, language, and processing speed.

In conclusion, the present review suggests that brain abnormalities (especially compensatory frontal hyperactivation) may begin quite early in the disease course, being more prominent shortly after chemotherapy with a partial recovery over time (Kesler et al., 2017a). The developmental trajectory of CRCI confirms the need to implement longitudinal designs including a pre-surgery assessment, since cross-sectional studies were not able to detect this pattern of recovery over time, supporting only the theory of brain abnormality in breast cancer survivors.

Further Directions

Although psychological factors such as anxiety and depression may also play a role in cognition, the lack of clinical symptoms or significant differences between groups may suggest that these factors do not account for this review's findings regarding brain abnormalities (Billiet et al., 2018; McDonald et al., 2012; McDonald et al., 2013). Menopausal status, age and fatigue seem to be the more prominent confounding factors. However, differences related to menopausal status or time related to endocrine therapy were not controlled in most studies, being an important limitation due to the small sample size resulting in insufficient power for this subgroup analysis.

Additionally, there is an increasing number of studies examining biological host factors and neuroinflammation pathways. The neuroinflammation hypothesis and the intermediary role of cytokines in pre- and post-chemotherapy cognitive impairment remains controversial (Ganz et al., 2013) deserving further research, since they may potentially impact the neurobiological basis of CRCI. Future studies should consider the fact that there might be several distinct factors implicating cognition, in these patients and, therefore, they should focus on developing longitudinal and multidisciplinary assessments converging neuropsychological tools, neuroimaging (e.g. task performance on cognitive tasks) and biological markers (e.g. proinflammatory cytokines and neurodegeneration endophenotypes). Such studies may positively impact patient care by determining the reasons why some patients are more vulnerable leading to the early identification of patients at a higher risk for developing CRCI. This may be an important step towards the development of preventive psychoeducational recommendations, targeted biological therapies and neuropsychological rehabilitation strategies.

Overall, the present review showed that neuroimaging techniques seem to be more sensitive than neuropsychological tools as an objective measure to assess CRCI. It also offered important insights for the consideration of functional neuroimaging as a relevant tool for CRCI clinical monitoring. Future studies should focus on assessing which fMRI specific tasks and techniques (e.g. rs-fMRI) can best assist this process of early detection and clinical follow-up over time, so it can become a more effective, less time consuming and cost-effective assessment tool.

Using the available and more sensitive neuroimaging tools such as fMRI to understand which patients are at risk of developing CRCI and further establish the subgroups that could benefit from remedial treatment strategies, such as cognitive training or psychotherapeutic programs, are promising research areas. The full functional recovery of patients in productive years could add important value to these interventions and diminish overall assessment costs.

Limitations and Strengths

The present review has an important limitation that needs to be addressed, since it included duplicate publications with partially repeated samples resulting (from some participants) being used, repeatedly, in more than one study. Only two studies presented unique samples (Deprez et al., 2014; Kesler et al., 2017b), which may have influenced this review's findings. The remaining duplicates (fifteen studies) presented data from multidisciplinary and multicentric research projects. Efforts were made to overcome this limitation by separately identifying functional and structural results, thus reducing data overlapping.

Additionally, only nine out of 16 included studies performed correlations between the results from the neuropsychological tests and brain-based measures. Without performance results from the neuropsychological tests, it is difficult to identify CRCI. This situation is a problem with some of the literature on this topic and, therefore, the results should be interpreted with caution. Future reviews on the topic should consider the inclusion of neuropsychological evaluations and its correlations with brain-based measures as a major goal.

Several strengths need to be acknowledged since the present review focused on reviewing longitudinal studies which contrasted with the conclusions from other cross-sectional studies, taking into consideration patients' sociodemographic

and clinical characteristics throughout the discussion, launching several hypotheses and suggesting future clinical and research directions.

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Compliance with Ethical Standards

Conflict of Interest The authors report no conflicts of interest.

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