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Cognitive alterations and brain functional changes following chemotherapy treatment in breast cancer patients: A systematic review on resting-state fMRI studies

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ABSTRACT

Cognitive dysfunctions and functional brain modifications are among the side effects reported by breast cancer patients that persist beyond the chemotherapy. This paper aims at synthesizing the evidence on cognitive and functional brain changes and their associations in breast cancer patients treated with chemotherapy. A systematic literature search was performed using PubMed, Ovid MEDLINE, Scopus, and Embase up to July 2022. Eligible studies evaluated adult women with breast cancer treated with systemic chemotherapy, that performed cognitive assessment and resting-state functional MRI. Methodological quality was assessed. Sixteen studies were included, with a total of 1054 female participants. All studies reported alterations mainly concerned the fronto-parieto-temporal system and specifically involved the disruption of the DMN. Consistent with these findings, BCPs showed changes in cognitive performance reporting dysfunctions in executive ability, memory, and attention. However, not all the studies found a significant association between functional brain alterations and cognitive dysfunction. Some limitations including lack of sample homogeneity and different methodological approaches were reported. This work highlighted the presence of cognitive dysfunctions and functional brain alteration in breast cancer patients treated with chemotherapy. This allows a greater awareness of the side effects, promoting better clinical management. However, further research is needed to investigate the cause-effect relationship between cognitive and functional alterations.

KEY POINTS

- A PROSPERO-registered systematic review identified 16 studies evaluating functional brain metrics and cognition during resting-state fMRI following chemotherapy in breast cancer patients.
- Cognitive performance, evaluated with neuropsychological tests or self-report tools, generally decreased after chemotherapy treatment.
- Alterations have been found in functional connectivity and brain activity, mainly related to the default mode network (DMN).
- Correlations among cognitive and functional brain changes were not univocally found.

KEYWORDS

Breast cancer; functional neuroimaging; cognition; chemotherapy; neuropsychology; resting-state

Introduction

Breast cancer (BC) is one of the most common cancers around the world and it is the most commonly diagnosed cancer in European women (Cardoso et al., 2019; Sung et al., 2021). In the last recent years, the incidence of BC in the population increased due to the gradual aging of the population (i.e., the risk of BC onset grows with increasing age) and due to the greater knowledge about the cancer disease and the promotion of specific screening tests. These improvements in early cancer detection and treatment efficacy have led to an unprecedented number of cancer survivors and, consequently, to different clinical needs including chronic and debilitating treatment-related side effects that can persist well beyond the active treatment. These possible unexpected treatment effects can have a detrimental impact on one's quality of life and even interfere with the medical decision making during the care process and with adherence to the treatment (Gorini & Pravettoni, 2011).

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Among these adverse effects, cognitive symptoms are commonly reported during and after the administration of chemotherapy (Argyriou et al., 2011; di Iulio et al., 2019). Indeed, chemotherapy-related neurotoxicity is associated with the release of pro-inflammatory cytokines, reduction of neurogenesis, and mitochondrial dysfunction that contribute to developing clinical difficulties such as mental cloudiness and weakened cognitive abilities (di Iulio et al., 2019; Joly et al., 2015; Staat & Segatore, 2005; Wefel et al., 2011, 2015). Moreover, compared to the healthy population, cancer patients exhibit a higher prevalence of cognitive difficulties reporting cognitive complaints as one of the major side effects (dos Santos et al., 2020). Specifically, cognitive dysfunctions exhibited in cancer patients are classified as "cancer-related cognitive impairment" (CRCI), objectively affecting up to 75% of patients during active treatment and approximately 30% of cancer survivors (di Iulio et al., 2019; dos Santos et al., 2020; Janelsins et al., 2017). CRCI mainly involves the impairment of multiple cognitive domains, including short-term memory, working memory, attention, executive functions, and/or information processing speed (di Iulio et al., 2019; dos Santos et al., 2020). Imaging studies on cancer patients confirmed the presence of brain changes associated with cognitive dysfunctions (Lange et al., 2019; Sousa et al., 2020). In breast cancer research, structural MRI studies have analyzed the post-treatment effects using both automated and manual approaches to quantify gray matter and white matter metrics, reporting mainly a reduction in gray matter volume and density and white matter microstructural alterations associated with altered cognitive performances in patients treated with chemotherapy compared to patients who did not receive chemotherapy and/or healthy controls (Lange et al., 2019; McDonald et al., 2013; Schroyen et al., 2022). Most of the reported associations between brain changes and cognitive dysfunctions involved frontal brain regions, mainly related to executive and amnestic processes (di Iulio et al., 2019; Li & Caeyenberghs, 2018; Wefel et al., 2015). Several functional brain modifications were also reported across brain networks mainly involving frontal, parietal, occipital, temporal, and cerebellar regions (Li & Caeyenberghs, 2018).

Despite increasing research on the consequences of breast cancer treatments, the mechanisms related to functional brain changes and their association with cognitive performance remains largely unknown. To the best of our knowledge, there are no studies that systematically evaluated this issue. Moreover, neuroimaging studies that investigated cognitive alterations in breast cancer patients (BCPs) showed great heterogeneity in the methodological approach adopted and small sample sizes (Schroyen et al., 2022). However, the adoption of the fMRI examination during the resting state allows to ensure better comparability between studies that are less vulnerable to variations in patient performances (Bruno et al., 2012; Lv et al., 2018). Therefore, this review aimed to synthesize the evidence on cognitive alterations and functional brain changes in a resting-state condition following chemotherapy treatment in BCPs.

Material and methods

Review question

To synthesize the evidence on cognitive alterations and functional brain changes in a resting-state condition of BCPs treated with chemotherapy.

Protocol

The latest PRISMA 2020 guidelines (Page et al., 2021) were used to draft this review and the related protocol was registered on PROSPERO in September 2022 (CRD42022358287).

Eligibility criteria

Eligibility criteria of studies were established considering the following criteria: (I) adult women with BC (>18 years) (II) scheduled for or treated with systemic chemotherapeutic agents, (III) performed a cognitive assessment (including neuropsychological tests or self-report questionnaires) (IV) in a resting-state functional magnetic resonance imaging (fMRI) study. Clinical populations with comorbidities that could compromise the cognitive status (i.e., other major neurologic or psychiatric disorders) and studies that adopted only active cognitive fMRI tasks were excluded.

Information sources

A systematic literature search was performed, without data restriction, using the following databases: PubMed, Ovid MEDLINE, Scopus, and Embase. The latest search was performed on July 1st, 2022.

Search strategy

The search strategy aimed to identify only published studies in the English language. An initial search was undertaken through PubMed to identify the Mesh terms related to the topic of the review. Three main medical descriptors were found: "breast cancer", "neuroimaging" and "cognition". These terms were further elaborated by identifying synonyms. Keywords were investigated in the titles and abstracts of relevant articles; this developed search strategy was applied for all the considered four databases (see Supplementary Material 1). Publications were excluded if they were conference abstracts, single-case studies, review articles, and studies with animal samples.

Selection process

All identified citations were uploaded into Mendeley and duplicates were removed. Two authors (L.C. and S.P.) independently assessed the eligibility of the articles. Firstly, both the authors read titles and abstracts of the potentially relevant studies identified in the search phase, and they classified them as "included", "excluded" or "maybe" following the eligibility criteria previously established. Then, the authors

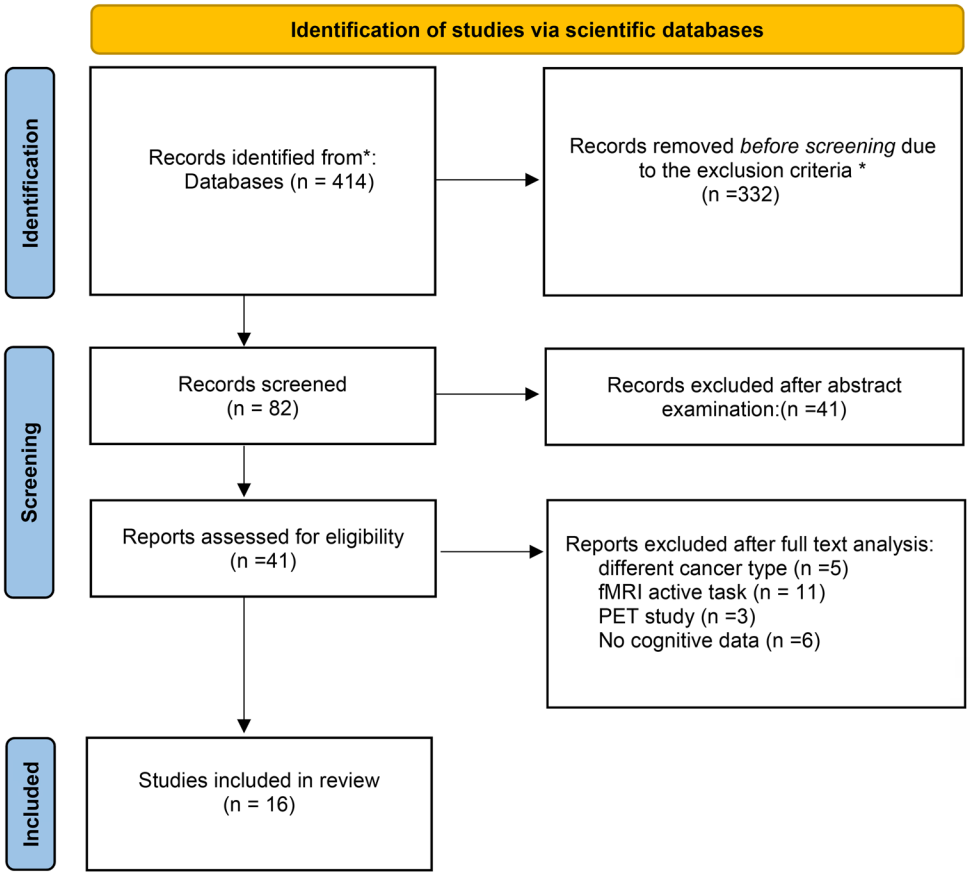

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.
* Conference paper, animal studies, paper not available in English, wrong population, duplicated studies, pediatric patients
** Wrong population and/or different clinical treatment

analyzed the full-text of all the studies marked as "included" and "maybe" for a more accurate step selection. In case of disagreement between the two authors, an agreement was achieved through a debate, or if necessary, by the opinion of a third independent reviewer (C.M.).

Data collection process

The main data were extracted from the selected studies by one reviewer (L.C), this process was then checked by a second reviewer (S.P). The key information extracted from each study included: authorship and publication year, population sampled, administered chemotherapeutic agents or protocol, characteristics of controls, timing of assessment, methods of neuroimaging, cognitive measures and main findings for cognition, neuroimaging, and their possible association.

Search results

The screening procedure is summarized in Figure 1. A total of 414 studies were identified from the four online databases (i.e., PubMed, Ovid MEDLINE, Scopus, and Embase). Following the removal of duplicates and the first screening of the title, abstract, and keywords, 82 studies remained. Forty-one studies were excluded. Finally, after the full-text examination, 16 studies remained and satisfied the inclusion criteria.

Risk of bias assessment

Methodological quality was assessed at the study level by two independent reviewers (L.C. and S.P.), using the risk of bias Down and Black checklist (Downs & Black, 1998). This instrument allowed us to assess the quality of reporting, internal validity, external validity, and statistical power. The scoring system of some items of the original checklist was modified to make it more suitable for the studies that we analyzed. In particular, according to other preview reviews (Hooper et al., 2008; Silverman et al., 2012), we changed the original score of item 5 (distributions of principal confounders) with a dichotomous score (Yes = 1 or No = 0), and we assigned a different classification to the item 27 (statistical power), according to the presence of a sample size analysis (Yes = 1) or not (No = 0).

Results

Study characteristics

A total of 1054 female participants were analyzed in this review, 618 (59%) of them were BCPs (M = 50.2; range = 20–82). In particular, 492 were BCPs treated with chemotherapy (CTx) and 126 were BCPs that did not receive chemotherapy treatment (no CTx). The remaining 436 (41%) participants were healthy controls (HC).

Only 5 articles (31%) mentioned the ethnicity of the participants. In particular, 3 studies explicitly reported the ethnicity, where 74% of BCPs were white and 26% were nonwhite (e.g., Afro-American, Asian). The remaining two studies identified 18% of BCPs as belonging to a minority group.

Eight studies (50%) provided information about the cancer state of the patients enrolled. Of the BCPs receiving CTx, 0.37% were in stage 0, 21% were in stage I, 53% were in stage II and 25% were in stage III. Of the BCPs with no CTx, 34% were in stage 0, 56% were in stage I, 9% were in stage II and 1% were in stage III.

About half of the studies (44%) mentioned the menopausal stage of participants. In particular, 51% of BCPs treated with CTx, 61% of BCPs with noCTx, and 41% of HC were postmenopausal.

Eight studies (50%) were conducted in Asia, 7 (44%) in America, and only one (6%) study was carried out in Europe. All the studies included were observational, and none of them had a randomized control design. Seven studies (44%) had a cross-sectional study design, 8 studies (50%) provided a longitudinal study design with a follow-up examination, and only one (6%) was a retrospective study. Between the longitudinal study design, 4 studies reported a long-term follow-up examination (more than 5 months), while the remaining 4 studies adopted a short-term follow-up investigation (up to one month). Eleven studies (69%) adopted a 2 arms design; in particular, 9 studies included healthy subjects as the control group whereas 2 studies used BCPs as the control group. Four (25%) studies adopted a 3 arms design, including both BCPs and healthy subjects as the control group. The remaining (6%) study did not adopt a control group. The sample size of the included studies varied from 21 to 183.

Methodological quality

A summary of the methodological quality assessment for the included studies is provided in the Supplementary Material 2. Scores on five categories of potential bias were obtained from each study, where lower values represent a higher risk of bias in that category. In particular, the "reporting bias" index showed a high score (mean (SD) 7.38 (0.77); range 0-10) indicating a lower level of risk of bias. The "external validity" (mean (SD) 2 (0); range 0-3) and "internal validity" (mean (SD) 3.75 (0.45); range 0-7) indexes reported medium scores; whereas the "selection bias" index showed low scores (mean (SD) 2.31 (0.08); range 0-6), revealing a higher level of risk of bias. Finally, the "statistical power" dimension resulted the weakest category, since all the studies included obtained the lower score (mean (SD) 0 (0); range 0-1) (see Figure 2). A summative score was calculated for each study (mean (SD) 16 (1.67); range 13-19) where lower global score represents a higher presence of bias that potentially compromise the methodological quality of the work.

Cognitive assessment and functional neuroimaging

Tools for the cognitive assessment

Nine studies (56%) included both standardized objective cognitive measures and subjective self-report tools. Six studies (37.5%) administered standardized objective cognitive measures whereas one study (6%) included only self-report tools (Kardan et al., 2019; Piccirillo et al., 2015). Only a few studies assessed global cognition using cognitive screening tests. Specifically, 3 studies used the Mini-Mental State Examination (MMSE), while 4 studies administered the Montreal Cognitive Assessment (MoCA).

The studies included in this review investigated the cognition of BCPs through the administration of a different battery of cognitive tests. In particular, two studies (13%) administered a single neuropsychological test, four studies (26.5%) adopted 2 neuropsychological tests, five studies (34%) used 3 different neuropsychological tests, and four studies (26.5%) administered 5 or more neuropsychological tests.

The main cognitive domains analyzed through neuropsychological tests, as shown in Figure 3, were executive functions (Bruno et al., 2012; Feng et al., 2020; Kesler et al., 2013, 2020; Luijendijk et al., 2022; Miao et al., 2016; Mo et al., 2017; Tao et al., 2017; Wang et al., 2016; Zheng et al., 2021) and attention/information processing speed (IPS) (Bai et al., 2021; Feng et al., 2020; Kesler et al., 2020; Miao et al., 2016; Mo et al., 2017; Phillips et al., 2022; Tao et al., 2017; Wang et al., 2016; Zheng et al., 2021), followed by amnestic abilities (Bai et al., 2021; Bruno et al., 2012; Chen et al., 2022; Feng et al., 2020; Kesler et al., 2013, 2020; Luijendijk et al., 2022; Mo et al., 2017; Phillips et al., 2022; Zheng et al., 2021), and language skills, less commonly evaluated. The self-report assessment mainly explored the complaints on global cognitive functioning, and specifically related to memory, attention, and executive function abilities (see Figure 3). The cognitive assessment and the main cognitive findings for each study are reported in Table 1.

Functional neuroimaging methodologies

Twelve studies (75%) adopted functional integration methods, while 4 studies (25%) used functional segregation methods. In particular, nine studies (56%) (Chen et al., 2022; Feng et al., 2020; Kardan et al., 2019; Kesler et al., 2013; Miao et al., 2016; Phillips et al., 2022; Piccirillo et al., 2015; Tao et al., 2017; Wang et al., 2016) analyzed resting-state functional connectivity (RS-FC) of brain networks, 2 studies (13%) (Bai et al., 2021; Mo et al., 2017) investigated the brain activity through the evaluation of Regional Homogeneity (ReHo), one study (Zheng et al., 2021) explored the Amplitude

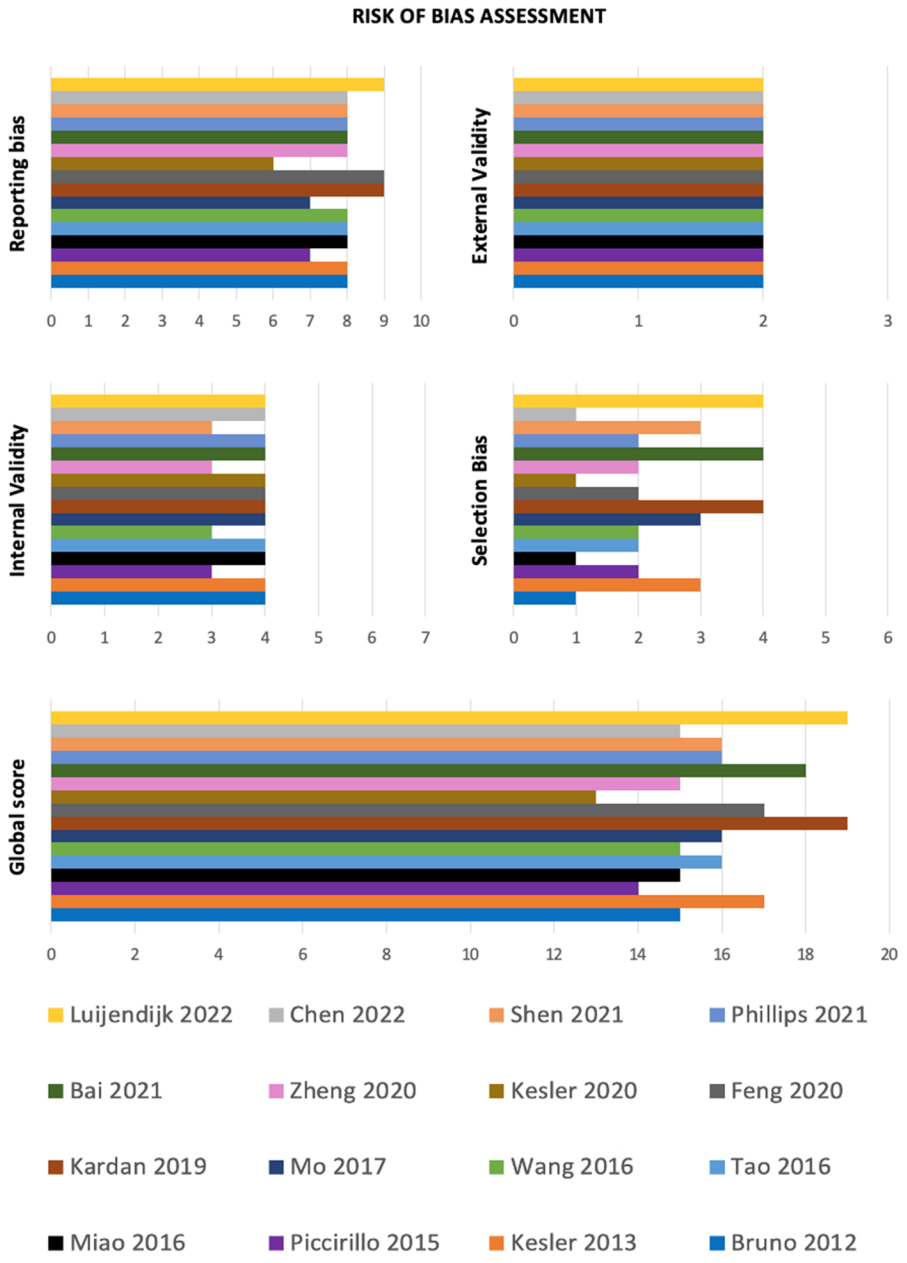

Figure 2. Risk of bias assessment.

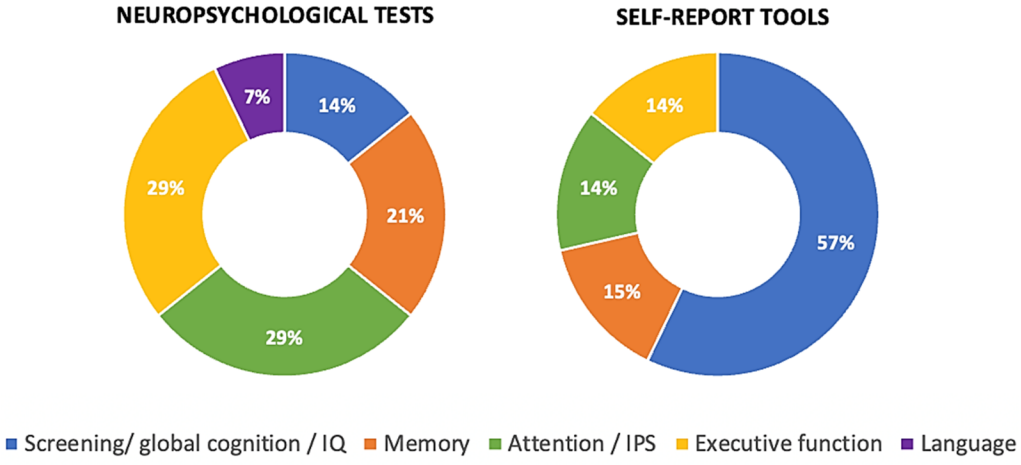

Figure 3. Graphic representation of cognitive tests adopted in the different studies.

Table 1. Cognitive and functional brain alteration in breast cancer patients after the administration of chemotherapy.

Author/year of publication	Study characteristics	Sample	Cognitive assessment	Main results	Association cognition/functional metrics
Bruno et al. (2012)	**Study design:** CS **Type of imaging:** Graph theory / functional correlation networks	34 BCP (stages I-IV) (Age: M = 55.16 ± 7.3) 27 HC (Age: M = 55.08 ± 9.12)	**Neuropsychological tests:** - WAIS-IV - D-KEFS Letter Fluency subtest - NAB Categories test - WCST - HVLT **Self-report tools:** - BRIEF - MMQ	**Cognition:** BCP vs HC showed lower performance at: - BRIEF - MMQ **Functional brain metrics:** Disrupted coordination among brain regions in BCPs after CTx BCP vs HC showed decrease - global clustering values - nodal degree in L amygdala, L caudate, R IFG, bilateral medial orbital frontal gyri, and bilateral STG. BCP showed additional networks hubs in bilateral lingual and occipital gyri, R parahippocampus and L ITG.	There were no significant associations between functional brain alteration and cognitive performance
Kesler et al. (2013)	**Study design:** CS **Type of imaging:** RS-FC of the DMN	31 BCP CTx (Age: M = 55 ± 7) 27 BCP noCTx (Age: M = 58 ± 7) 27 HC (Age: M = 56 ± 9)	**Neuropsychological tests:** - WAIS Matrix Reasoning and Information - D-KEFS Letter Fluency - NAB categories test - HVLT-R - WCST **Self-report tools:** - BRIEF - MMQ	**Cognition:** There were no significant group differences on neuropsychological tests **Functional brain metrics:** BCP CTx vs HC/BCP noCTx reported greater difficulties in: - BRIEF - MMQ Abnormal DMN connectivity was associated with BCP CTx	In BCP CTx distance from the hyperplane was negatively correlated with MMQ within both BCP no CTx (r=-0.40) and HC (r=-0.68)
Piccirillo et al. (2015)	**Study design:** CS **Type of imaging:** RS-FC	15 BCP subjectively reported CI (Age = 54; min-max = 36–69) 13 BCP subjectively reported CP (Age = 52 min-max = 40–67)	**Self-report tools:** - CFQ - GRC	**Functional brain metrics:** CI BCP vs CP BCP showed weaker FC between - L fronto-parietal region/ R parietal region Altered FC of brain regions involved in DMN	Negative association between correlation strength and GRC in CI BCP
Miao et al. (2016)	**Study design:** CS **Type of imaging:** RS-FC	22 BCP (stages II–III) (Age: M = 43.68 ± 6.81) 22 HC (Age: M = 44.5 ± 7.44)	**Neuropsychological tests:** - MoCA - Stroop tests (Stroop-C, Stroop-W, Stroop-I)	**Cognition:** BCP vs HC showed significantly worse performance at: - Stroop tests **Functional brain metrics:** BCP vs HC exhibited lower connectivity of the DMN In the MTL: - vMPFC–Rsp - pIPL–vMPFC - pIPL-Rsp In the dMPFC subsystem - pIPL-PHC - dMPFC-TempP	BCP showed a negative correlation between FC of the vMPFC-Rsp in MTL subsystem and RT in: - Stroop-C (p = .007, r = −.188) - Stroop-W (p = .044, r = −.391) The connectivity of pIPL-Rsp was negatively correlated with the RT of Stroop-C (p = .040, r = −.400)

(*Continued*)

Table 1. Continued.

Author/year of publication	Study characteristics	Sample	Cognitive assessment	Main results	Association cognition/functional metrics
Wang et al. (2016)	**Study design:** CS **Type of imaging:** RS-FC	32 BCP (stage II / III) (Age: M = 44.19 ± 6.61) 24 HC (Age: M = 43.25 ± 8.45)	**Neuropsychological tests:** - MoCA - Stroop tests (Stroop-C, Stroop-W, Stroop-I)	**Cognition:** BCP vs HC had significantly worse performance in - Stroop-C - Stroop-W - Stroop-I **Functional brain metrics:** BCP vs HC displayed lower FC in the - L STG - R IFG - R MFG increased FC in the - R MTG - R precuneus	In BCP the altered FC between the R dLPFC – R IFG was correlated to the worse performance on the Stroop-I (r= −0.376, P = 0.0339).
Tao et al. (2017)	**Study design:** CS **Type of imaging:** RS-FC	33 BCP (stages I–III) (Age: M = 39.48 ± 6.32) 31 HC (Age: M = 39 ± 7.29)	**Neuropsychological tests:** - MMSE (screening) - Stroop tests (Stroop-C, Stroop-W, Stroop-I) - TMT	**Cognition:** BCPvsHC showed lower scores on: - Stroop-I - TMT B BCPvsHC showed higher scores on: - Stroop-W - TMT A **Functional brain metrics:** BCP vs HC showed lower FC in: - L PoCG - L PCG - R STG - R cingulate gyrus - R MFG	BPC showed negative correlation between the RT on the TMT and the FC strength between: - the PCC and R MFG (r= −.565, p= 0.001) - the PCC and R cingulate gyrus (r= −.509, p = 0.002). BPC showed negative correlation between - the RT on the Stroop-I and the FC strength between - the PCC and R MFG (r= −.479, p= 0.005).
Mo et al. (2017)	**Study design:** LS - T0: baseline - T1: 2/3week after CTx **Type of imaging:** ReHo	19 BCP (Age: M = 43.1 sd = 8.8) 11 HC (Age: M = 42.4 ± 5.3)	**Neuropsychological tests:** - MoCA - WAIS (III) Digit Symbol - AVLT **Self-report tools:** FACT-COG	**Cognition:** No cognitive difference between BCP and HC at T0 T1 BCP vs T0 BCP showed worse performance in the AVLT and FACT-COG **Functional brain metrics:** T1 BCP vs T0 BCP showed significant: increase in ReHo in the - cerebellum - R orbitofrontal area decrease in ReHo in - R orbitofrontal area - R MTG and STG - R subcentral area - L DLPFC - PCG.	T1 BCP vs T0 BCP showed - a positive correlation between attention and ReHo changes in L DLPFC (r= 0.486) - a negative correlation between short term memory and ReHo changes in PCG (r= -0.502)

(*Continued*)

Table 1. Continued.

Author/year of publication	Study characteristics	Sample	Cognitive assessment	Main results	Association cognition/functional metrics
Kardan et al. (2019)	**Study design:** LS - T0: baseline - T1: 1 month - T2: 7 months **Type of imaging:** RS-FC	18 BCP CTx (Age: M = 49.22 ± 11.13) 22 BCP no CTx (Age: M = 53.82 ± 8.18) 22 HC (Age: M = 51.13 ± 8.79)	**Neuropsychological tests:** - Digit span (DSF and DSB) **Self-report tools:** - AFI	**Cognition:** T1 BCP CTx vs T0/T2 BCP CTx reported poorer AFI score and lower DSF and DSB **Functional brain metrics:** T1 vs T0 BCP FC decreases in - parietal and frontal regions T2 vs T1 BCP FC increases (especially BCP CTx) in parietal and frontal regions	There were no significant associations between functional brain alteration and cognitive performance.
Feng et al. (2020)	**Study design:** LS - T0: baseline - T1: 5/6 months **Type of imaging:** RS-FC	29 BCP (stages I-III) (Age: M = 49.27 ± 9.3) 24 HC (Age: M = 47.56 ± 9.5)	**Neuropsychological tests:** - AVLT - Stroop tests (Stroop-C, Stroop-W, Stroop-I) - DST - LTT - SDT - VFT - NCT-A - MMSE	**Cognition:** BCP vs HC showed lower cognitive performance at LTT and Stroop-W. T1 BCP vs T0 BCP had worse cognitive performance in - LTT - Stroop-C - AVLT **Functional brain metrics:** T0 BCP vs T0 HC showed no FC differences T1 BCP vs T0 BCP showed increased FC changes: - L/R hippocampus - L insula - L anterior hippocampal - L MTG/ pSTG - L heschl gyri/insula - R posterior hippocampal - L STG/ L heschl gyri	There were no correlations between neuropsychological test changes and hippocampal-based FC alteration
Kesler et al. (2020)	**Study design:** RPS **Type of imaging:** Connectome	80 BCP 103 HC (82 fMRI) (Age: M = 49 ± 13)	**Neuropsychological tests:** - CTMT - D-KEFS Letter Fluency test - RAVLT **Self-report tools:** - BRIEF-A	They identified 3 biotypes of BCPs **Cognition:** - Biotype 1 vs HC showed lower performance across cognitive tests - Biotype 3 vs HC showed lower performance on 4/5 tests - Biotype 2 vs HC showed lower performance only on Letter Fluency **Functional brain metrics:** - Biotype 1 vs HC demonstrated higher medial frontal network disruption and lower DMN dysconnectivity - Biotype 2 vs HC showed higher hyperconnectivity affecting 7/8 networks, the subcortical/cerebellar and motor networks - Biotype 3 vs HC showed greater disruption of DMN and alteration of subcortical /cerebellar networks Medial frontal and subcortical /cerebellar networks were the most commonly disrupted across the biotypes vs HC.	N/A

(*Continued*)

Table 1. Continued.

Author/year of publication	Study characteristics	Sample	Cognitive assessment	Main results	Association cognition/functional metrics
Zheng et al. (2021)	**Study design:** LS - T0: 6 months before CTx - T1: 1 month after CTx **Type of imaging:** ALFF	21 BCP (Age: M = 50.14 ± 13.12)	**Neuropsychological tests:** - NCT-A - Digital Breadth Test forward and backward - Stroop tests (Stroop-C, Stroop-W, Stroop-I) - Numeric Symbol Test - AVLT - MoCA	**Cognition:** T1 BCP vs T0 BCP showed lower performance in the: - Stroop-W and Stroop-I - Digit Breadth Reverse test - AVLT **Functional brain metrics:** T1 BCP vs T0 BCP showed increased ALLF of: - L ITG - bilateral MTG - L upper temporal gyrus - bilateral precuneus	There is no correlation between cognitive scores for the ALFF value
Bai et al. (2021)	**Study design:** LS - T0: baseline - T1: after CTx **Type of imaging:** ReHo	19 BCP (Age: M = 43.1 ± 8.8) 11 BCP controls	**Neuropsychological tests:** - AVLT - DSp2 **Self-report tools:** - FACT-COG	**Cognition:** T0 BCP vs T0 controls had no significant difference in cognitive performance T1 vs T0 BCP showed lower cognitive performance in AVLT and FACT-COG **Functional brain metrics:** T1 vs T0 no significant difference in ReHo values in the patients controls. T1 vs T0 BCP, a significant change in ReHo in some brain regions - increased the value of ReHo in L/R orbital frontal dorsolateral prefrontal cortex - decreased in cerebellum front leaf, leaf cerebellar, R temporal gyrus and the MFG	There is a correlation between - the changes in the DSp2 and the changes in the ReHo value of the L MFG (r = 0.486) - the change of AVLT and the change of the ReHo value of the central anterior gyrus (r= −0.502) [not statistical significance after false discovery rate correction].
Shen et al. (2021)	**Study design:** CS **Type of imaging:** mean fractional ALFF (mfALFF) mean ReHo (mReHo)	32 BCP CTx (Age: M = 49.9 ± 6.3) 32 BCP no CTx (Age: M = 48.6 ± 6.7) 46 HC (Age: M = 43.5 ± 7)	**Neuropsychological tests:** - MMSE **Self-report tools:** - CAMS-R	**Cognition:** BCP CTx and BCP no CTx showed no significant differences in the MMSE and CAMS-R scores. **Functional brain metrics:** In the fronto-parietal lobe: - BCP CTx and BCP no CTx vs HC showed significantly increased mfALFF BCP no CTx vs BCP CTx showed greater mfALFF - BCP CTx vs HC showed greater mfALFF In the occipital lobe - BCP CTx and HC vs BCP no CTx showed greater mfALFF In the fronto-parietal lobe - HC vs BCP CTx showed greater mReHo - BCP CTx vs BCP no CTx showed greater mReHo	MMSE and CAMS-R scores showed a positive correlation with mfALFF in the occipital lobe and a negative correlation with mfALFF in the fronto-parietal lobe. MMSE and CAMS-R scores showed a positive correlation with mReHo in the fronto-parietal lobe.

(*Continued*)

Table 1. Continued.

Author/year of publication	Study characteristics	Sample	Cognitive assessment	Main results	Association cognition/functional metrics
Phillips et al. (2022)	**Study design:** LS - T0: baseline - T1: 1 month after CTx - T2: 1 year after CTx **Type of imaging:** FC	43 BCP (stage I–III) (Age: M = 49 ± 8.9) 50 HC (Age: M = 50 ± 10)	**Neuropsychological tests:** - RAVLT - CTMT - COWA	**Cognition:** T1 BCP vs T0 BCP showed lower scores in RAVLT, CTMT and COWA T2 BCP vs T0 BCP demonstrated lower RAVLT, CTMT and COWA performances. Both BCP and HC groups tended to improve cognitive performance at T2 **Functional brain metrics:** T1 BCP vs HC revealed multiple local differences, showing higher or lower edge centrality T2 BCP vs HC showed significantly - higher global efficiency and path length - lower centrality for multiple edges	Lower interference memory score was associated with higher edge centrality between L superior orbital frontal and R angular gyri.
Chen et al. (2022)	**Study design:** LS - T0: baseline - T1: 1 month after CTx **Type of imaging:** FNC of DMN	19 BCP (Age: M = 66.6 ± 5.24) 14 HC (Age: M = 68.1 ± 5.69)	**Neuropsychological tests:** psm from NIH Toolbox Cognition Battery	**Cognition:** BCP vs HC had no significant difference in cognitive performance **Functional brain metrics:** The BCP showed in the DMN weaker FNC from: - mPFC - R frontal lobe - R temporal lobe - L/R hippocampus stronger FNC from: - L parietal lobe - R parietal lobe The BCP showed in the ACC subnetwork - weaker FNC to the anterior region at T0 - stronger FNC to the posterior region than the HC group Longitudinal changes BCP T1 vs T0 in DMN showed increased FNC in - L/R frontal lobe - R temporal lobe decreased FNC in: - mPFC, - L temporal lobe - retro splenial BCP showed in the ACC subnetwork - increased FNC to the anterior region - decreased FNC to the posterior region In BCPs vs HC, the DMN FC subnetworks were significantly more diminished from T0 to T1.	There were no correlations between cognitive scores and FNC.

(*Continued*)

Table 1. Continued.

Author/year of publication	Study characteristics	Sample	Cognitive assessment	Main results	Association cognition/functional metrics
Luijendijk et al. (2022)	**Study design:** LS - T0: baseline - T1: 6 months **Type of imaging:** Dynamic FC (dFC) of DMN and FPN	34 BCP CTx (Age: M = 49.2 ± 9.3) 32 BCP no CTx (Age: M = 50.8 ± 7.1) 35 HC (Age: M = 49.7 ± 10.3)	**Neuropsychological tests:** - HVLT-R - TMT-B - NART	**Cognition and Functional brain metrics:** No significant group differences or changes over time in cognitive and neuroimaging outcomes were found in BCPs and HC.	BCP no CTx at T1 - increase in DMN-dFC was associated with an increase in memory function. BCP CTx and HC at T1 - increase in DMN-dFC was associated with a decrease in memory function.

WAIS-IV = Wechsler adult intelligence scales, D-KEFS = Delis-Kaplan executive function system, BRIEF = behavioral rating inventory of executive function, WCST = Wisconsin card sorting test, HVLT-R = Hopkins verbal learning test revised, MMQ = multifactorial memory questionnaire ability Scale, CFQ = cognitive failures questionnaire, GRC = global rating of cognition, TMT = trail making tests, AVLT = auditory verbal learning test, FACT-COG = functional assessment of cancer therapy-cognitive Function, CTMT = comprehensive trail making test trails, MoCA = montreal cognitive assessment scale, MMSE = mini-mental state examination, CAMSR = cognitive and affective mindfulness scale-revised, NIH = national institutes of health toolbox cognition battery, NART = national adult reading test, DST = digit symbol test, LTT = line tracing test, SDT = serial dotting test, VFT = verbal fluency test, NCT-A = number connection test A, COWA = Controlled Oral Word Association, PSM = Picture Sequence Memory, NIH = National Institutes of Health, NAB = Neuropsychological Assessment Battery, Stroop-C = Stroop color test, Stroop-W = Stroop words test, Stroop-I = Stroop interference test, RT = response time, AFI = Attentional Function Index, FC = functional connectivity, dMPFC = dorsal medialprefrontal cortex, MTL = medial temporal lobe, vMPFC = ventral dorsal medial prefrontal cortex, pIPL = posterior inferior parietal lobule, Rsp = retrosplenial cortex, PHC = parahippocampal cortex, MFG = middle frontal gyrus, PCC = posterior cingulate cortex, IFG = inferior frontal gyrus, pSTG = temporal pole of superior temporal gyrus, MTG = middle temporal gyrus, ITG = inferior temporal gyrus, BCP = breast cancer patients, PoCG = postcentral gyrus, PCG = precentral gyrus, STG = superior temporal gyrus, DLPFC = dorsolateral prefrontal cortex, CTx = chemotherapy, ReHo = regional homogeneity, RS-FC = resting state functional connectivity, FNC = functional network connectivity, HC = healthy controls, CS = cross-sectional study, LS = longitudinal study, RPS = retrospective study, CI = cognitively impaired, CP = cognitively preserved, L = left, R = right, TempP = temporal pole, ALFF = amplitude of low frequency fluctuations, DMN = default mode network, FPN = fronto-parietal network.

of Low-Frequency Fluctuations (ALFF) to assess the activity in local brain regions, and one study (Shen et al., 2021) analyzed both ReHo and ALFF. One study (Luijendijk et al., 2022) investigated dynamic functional connectivity (dFC), 1 study (Bruno et al., 2012) adopted graph analysis to assess RS functional connectivity network, and one study (Kesler et al., 2020) focused on the whole-brain functional connectivity (i.e., connectome).

The RS-FC of the brain networks was the most used neuroimaging methodology for both cross-sectional (71%) and longitudinal (50%) study designs. The retrospective study, instead, adopted a whole-brain functional connectivity.

All the studies reported functional brain alterations in BCPs at rest following the administration of chemotherapy, which mainly involves fronto-parietal regions. In particular, twelve studies (75%) reported functional brain alteration in brain regions directly involved or associated with the Default Mode Network (DMN), highlighting the association of this functional network with cancer treatments.

Despite these findings, several studies did not report univocal results showing both a reduction and increase in functional brain activity (Bai et al., 2021; Chen et al., 2022; Kardan et al., 2019; Mo et al., 2017; Phillips et al., 2022; Wang et al., 2016) in CTx BCPs. The specific functional brain findings of each study were reported in Table 1.

Relationship between cognitive and functional neuroimaging measures

Five studies (31%) did not find any statistically significant associations between functional brain changes and cognitive performance, whereas one study (6%) did not report data related to a possible association. The remaining ten studies (63%) showed statistically significant correlations between functional brain alterations and cognitive findings, mainly involving an association between functional brain disruption and changes in attention, executive function, and memory performances.

Six (86%) of the cross-sectional studies reported significant associations between cognitive performance and functional brain activity in BCPs receiving CTx compared to control groups. In particular, one study showed negative correlations between hyperplane distance and self-rated memory ability (Kesler et al., 2013). Three studies showed negative correlations between lower FC and attention and executive function performances (Miao et al., 2016; Tao et al., 2017; Wang et al., 2016). One study reported a negative correlation between the functional connection strength and the global rating of cognition (Piccirillo et al., 2015). Finally, one study found that objective and subjective cognitive performances were positively correlated with both amplitudes of low frequency fluctuations (ALFF) and regional homogeneity (ReHo) (Shen et al., 2021).

Four (50%) of the longitudinal studies reported significant associations between cognitive performance and functional brain activity in BCPs receiving CTx compared to control groups. Two studies found positive correlations between ReHo changes and attentive performance (Bai et al.,

2021; Mo et al., 2017), whereas changes in ReHo were negatively associated with memory performance (Bai et al., 2021; Mo et al., 2017). A negative association was found between memory score and edge centrality of frontal brain regions (Phillips et al., 2022). Finally, a negative association was found between the dynamic functional connectivity of DMN and memory performance (Luijendijk et al., 2022).

Specific associations between functional brain findings and cognitive performance of each study were reported in Table 1.

Discussion

During the last decade, the interest related to brain and cognitive changes as a possible consequence of pharmacological cancer treatments has grown. In particular, chemotherapy is used to treat many types of cancers but has been associated with neurotoxicity, which is characterized by a reduction of neurogenesis, mitochondrial dysfunction, and inflammation (di Iulio et al., 2019; Schroyen et al., 2022). Specifically, chemotherapeutic treatment is thought to cause several adverse effects, including structural and functional brain alterations and cognitive deficits (Sousa et al., 2020).

In the literature, a minority of studies focused on the functional consequences, compared to the structural alterations. However, the functional aspects play a crucial role since they allow one to explore information processing capabilities and global brain information integration even when the patient is in a resting condition. Indeed, the level of spontaneous neuron activity in specific brain regions during the resting state is closely related to the strength of the activity during an active task, reflecting the brain's ability to face an external request (Friston, 2011; Zheng et al., 2021).

To the best of our knowledge, this study was the first review to synthesize functional brain imaging changes, in a resting state condition, and cognitive alterations of BCPs treated with chemotherapy and to focus attention on their association.

From our review emerged the presence of functional brain alterations in those BCPs treated with chemotherapy, compared to control groups or normative data. Several studies reported disruption of the functional connectivity, or altered brain activity, mainly located in the frontal system, with the involvement of parietal and temporal lobes.

Specifically, several studies identified a significant role of the DMN, mentioning a disruptive functional organization of the network itself (Chen et al., 2022; Kesler et al., 2013; Luijendijk et al., 2022; Miao et al., 2016; Phillips et al., 2022; Piccirillo et al., 2015; Zheng et al., 2021) or reporting functional alterations of directly associated brain areas.

The DMN is a large-scale brain network consisting of the medial and lateral parietal cortex, medial prefrontal cortex (MPFC), and medial and lateral temporal cortex (Raichle, 2015). These cortical areas are usually engaged in different pivotal cognitive functions such as cognitive flexibility, memory, attention, elaboration of emotional response, social behavior, and mood control (Raichle, 2015).

Due to the involvement in spontaneous intrinsic brain activity, the DMN has been highly investigated in literature (Uddin et al., 2008). The DMN is also particularly susceptible to drug toxicity, and disease progression (Kesler, 2014), and it is involved in the normal aging process (Ferreira & Busatto, 2013) and in a variety of neuropsychiatric disorders, such as Schizophrenia (Guo et al., 2014), Mild Cognitive Impairment (MCI) (Qi et al., 2010; Yuan et al., 2021), Alzheimer's disease (Balthazar et al., 2014) and Alcohol use disorder (Gerhardt et al., 2022). Interestingly, similar DMN dysfunction has been shown in other types of oncological patients following chemotherapy treatment such as lung cancer (Liu et al., 2022).

According to previous studies, damage to large-scale brain networks reflects alterations in the underlying structural connectivity (Kesler et al., 2013; Wang et al., 2016). Chemotherapy treatment in BCPs is associated with diffuse injury to the gray matter tissues and white matter pathways integrity that does not allow efficient communication within brain areas (Deprez et al., 2013; Kesler et al., 2013; Schroyen et al., 2022). This mechanism identified as "disconnection syndrome" (Catani & Mesulam, 2008) has already been evidenced in other syndromes such as multiple sclerosis (Dineen et al., 2009) or Alzheimer's Disease (Yuan et al., 2021), also having consequences on patients' cognitive performances.

Consistently, the BCPs treated with chemotherapy showed deficits in neuropsychological performance, which reflected the brain functional alterations. Indeed, several studies included in this review identified cognitive dysfunctions that mainly involved executive ability, memory, attention, and learning ability, which are strictly associated with the fronto-parieto-temporal system. Specifically, executive function performances seem particularly damaged in BCPs, due to the massive involvement of the prefrontal cortex. The executive function system is crucial because it has a role in the control of complex cognition and the management of other cognitive processes related to cognitive flexibility, working memory, shifting of attention, goal-directed behavior, and the ability to make decisions (McCabe et al., 2010).

Furthermore, a few studies included in this review explored the BCPs' cognitive dysfunctions through the use of self-report tools. Indeed, subjective cognitive complaints are frequently reported by oncological patients following cancer treatments (dos Santos et al., 2020; Janelsins et al., 2017; Lange et al., 2019). These findings showed that BCPs communicated major difficulties in memory and executive function abilities, which are in line with those found on neuropsychological assessment.

However, some of the studies analyzed did not identify cognitive differences between BCPs treated with chemotherapy and the control group (Chen et al., 2022; Kesler et al., 2020; Luijendijk et al., 2022; Shen et al., 2021). This result may not mean the absence of cognitive impairments but may represent the adoption of compensatory strategies. Indeed, early cognitive deficits can be balanced by the involvement of additional brain areas for the maintenance of cognitive functioning (Stern et al., 2019). Interestingly, the alteration of functional connectivity found in BCPs after chemotherapy

was not unidirectional, together with widespread decreased functional brain network connectivity, some studies found increased activity in several brain areas (Bai et al., 2021; Chen et al., 2022; Kardan et al., 2019; Mo et al., 2017; Shen et al., 2021; Wang et al., 2016). This discrepancy between functional alterations may be explained as a compensatory mechanism, where some brain areas increase their activity to counterbalance deficits in other cortical regions or decreased cognitive functioning (di Iulio et al., 2019; Liu et al., 2022). Accordingly, other clinical populations such as MCI patients (Qi et al., 2010) and lung cancer patients (Liu et al., 2022) showed an opposite trend of functional alteration, supporting the presence of a compensatory process.

Another interesting evidence from different retrieved studies (Kardan et al., 2019; Zheng et al., 2021) revealed that chemotherapy treatment is associated with a reduction of the overall network efficiency, as well as cognitive alterations, that are marked just after drug administration and gradually decrease months after chemotherapy. This finding suggested a transient impact of the adverse effect of chemotherapy administration, without however returning to the pretreatment level; indeed, widespread brain alterations have been found even years after treatments (Kesler, 2014).

Finally, despite the findings of functional brain alterations and consistent cognitive dysfunctions both related to the fronto-parieto-temporal system, the evidence related to their association was mixed in BCPs following chemotherapy. In addition, several studies did not find a statistically significant correlation between these adverse symptoms (Bruno et al., 2012; Chen et al., 2022; Feng et al., 2020; Kardan et al., 2019; Zheng et al., 2021), suggesting that those modifications were not strictly connected. However, in the current state, it is not possible to conclude the cause-effect relationship between cognitive dysfunction and functional neuroimaging alterations following drug administration.

Limitations

Several limitations of the studies included in this review should be mentioned. First, neuroimaging studies showed great heterogeneity in the methodological approach adopted. Overall the studies adopted different instruments and criteria for the classification of cognitive impairment, not allowing a rigorous investigation of the cognitive dysfunctions. In addition, self-report tools are often used instead of neuropsychological tests, not allowing an objective quantification of the decline in cognitive performance.

Moreover, the characteristics of the patients' sample lack homogeneity in different demographical variables, such as age and education level. Both variables are indeed relevant for the evaluation of brain and cognitive assets. In particular, aging is a fundamental issue to take into consideration since it is related both to physiological brain alterations, involving the fronto-parietal system (Ferreira & Busatto, 2013; Oschwald et al., 2019), and to the decline of some cognitive domains, such as memory and executive functions (Oschwald et al., 2019) that could mislead the interpretation of more specific results.

Another main limitation of the included studies concerns the small sample sizes. From the Risk of bias assessment emerged that the included studies exhibited a great weakness in the statistical power, where none of them provided a power analysis to support the sample size adopted. This limitation is particularly relevant since it could affect the quality and the generalizability of the findings. Furthermore, some of the studies analyzed did not seem to take into consideration certain possible confounders that could influence cognitive performance, such as the presence of concomitant therapies or personal characteristics of the subjects involved (e.g., menopausal status). In addition, it is not very clear how the cognitive data are treated, and whether any correction was applied (e.g., age/schooling, error associated with multiple tests of significance) to minimize the possibility of bias.

Lastly, several studies adopted a cross-sectional design that does not allow a comparison between a baseline condition and after-treatment follow-up, making uncertain the attribution of clinical alteration to the treatment. However, evidence on the trajectory of changes within years is still lacking.

Implications for future research

These findings could suggest a potential contributor of chemotherapy to the insurgence of cognitive alterations in BCPs. However, considering the limitations found in the different studies included in this review, it is important to take into account certain aspects to shed light on this issue.

Future studies should set up longitudinal designs that allow to define cognitive and brain modifications related to chemotherapy and disease progression and follow their evolution over time. Moreover, more attention must be paid to the constitution of the study sample, with adequate power analysis which makes it possible to determine whether a result is due to chance or whether it is authentic and meaningful. Finally, to ensure greater accuracy and allow better comparison of results, future research should adopt the specific guidelines published (Joly et al., 2015; Lange et al., 2019; Wefel et al., 2011) regarding the cognitive assessment and the recommended classification of cognitive impairment. The application of these guidelines will also make it possible to set up meta-analysis that synthetize the main data obtained from the different studies; which could not currently be performed due to statistical heterogeneity, different study design, and outcome measurement.

Implications for future practice

The differences found in cognition highlight the importance of including the assessment of cognitive functioning in daily clinical practice and introducing neuropsychological tests specifically designed for oncological patients, allowing to detect early cognitive difficulties. A longitudinal evaluation of the cognitive functions on quality of life, job, and social functions might shed light on the impact of such alterations on real life. Moreover, effective communication with healthcare professionals would promote health literacy among patients, having

greater awareness of their clinical status and reporting those symptoms that could usually be overlooked (Cutica et al., 2014; Pravettoni & Gorini, 2011). Greater awareness of the mechanisms relating to the onset of these adverse symptoms would allow greater attention to personalized and patient-oriented medicine through the setting of timely interventions.

Conclusion

BCPs can experience cognitive dysfunctions and alterations in functional brain activity following chemotherapy treatment. The modifications, found during the resting condition, mainly concerned the fronto-parieto-temporal system and specifically involved the disruption of the DMN. Consistent with these alterations, BCPs showed changes in cognitive performance reporting dysfunctions in executive ability, memory, attention, and learning ability. Nevertheless, not all the studies included found a significant association between functional brain alterations and cognitive dysfunction. These findings could suggest a potential contributor of chemotherapy to the insurgence of cognitive alterations in BCPs. However, acknowledging several limitations in the methodological approaches and sample characteristics of the studies included in this review, and the lack of available longitudinal data, at the current state, further research are needed to better investigate the cause-effect relationship to the cognitive dysfunction and functional neuroimaging alterations following drug administration.

Disclosure statement

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