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Review article

Chemo-brain: An activation likelihood estimation meta-analysis of functional magnetic resonance imaging studies

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ABSTRACT

Adults with non-central nervous system (CNS) cancers frequently report problems in attention, memory and executive function during or after chemotherapy, referred to as cancer-related cognitive dysfunction (CRCD). Despite numerous studies investigating CRCD, there is no consensus regarding the brain areas implicated. We sought to determine if there are brain areas that consistently show either hyper- or hypo-activation in people treated with chemotherapy for non-CNS cancer (Chemo+). Using activation likelihood estimation on brain coordinates from 14 fMRI studies yielding 25 contrasts from 375 Chemo+ and 429 chemotherapy-naive controls while they performed cognitive tasks, the meta-analysis yielded two significant clusters which are part of the frontoparietal attention network, both showing lower activation in Chemo+. One cluster peaked in the left superior parietal cortex, extending into precuneus, inferior parietal lobule, and angular gyrus. The other peaked in the right superior prefrontal areas, extending into inferior prefrontal cortex. We propose that these observed lower activations reflect a dysfunction in mobilizing and/or sustaining attention due to depletion of cognitive resources. This could explain higher level of mental fatigue reported by Chemo+ and why cancer survivors report problems in a wide variety of cognitive domains.

1. Introduction

Cancer-related cognitive dysfunction (CRCD) refers to diminished thinking abilities, such as problems with attention, memory and multitasking, that can persist in cancer patients long after treatment is complete. The etiology of CRCD is not well understood but is considered to be multifactorial, including disease-, treatment- and patient-related factors (Wefel et al., 2015). CRCD is reported by breast cancer survivors not treated with chemotherapy (Chemo–), but symptoms are more prevalent in those who were (Chemo+) (Ahles and Root, 2018; Bernstein et al., 2017; Kohli et al., 2007; Mandelblatt et al., 2013; Scherling and Smith, 2013; van Dam et al., 1998; Wefel et al., 2010; Yao et al., 2017a, b). CRCD is associated with poor psychosocial and occupational functioning, including participating in and accomplishing meaningful goals (Boykoff et al., 2009). Cognitive impairment is also reported in adults treated with chemotherapy for other types of cancer, including colorectal (Vardy et al., 2015), gynecologic (Correa et al., 2017), head and neck (McDowell et al., 2019; Welsh et al., 2014; Zer et al., 2018), lung (Simo et al., 2015), lymphoma (Zimmer et al., 2015), multiple myeloma (Ramsenthaler et al., 2016), prostate (Gonzalez et al., 2015; Sun et al., 2018), testicular (Chovanec et al., 2018; Stouten-Kemperman et al., 2018) and thyroid (Saeed et al., 2019).

Neurocognitive assessment has provided valuable data to characterize broad patterns of CRCD (Freeman and Broshek, 2002; Scherwath et al., 2006; Vardy et al., 2007). Still, ongoing inconsistencies within this literature highlight the difficulty capturing often subtle cognitive abnormalities that nonetheless have a detrimental impact on quality of life. Furthermore, behavioral studies find little to no correlation between neurocognitive test scores and self-reported cognitive impairment (Bender et al., 2008; Biglia et al., 2012; Bray et al., 2018; Edelstein and Bernstein, 2014). A better understanding of the neurobiology underlying CRCD could shed light on these discrepancies and inform therapeutic approaches that could be beneficial for reducing the impact of chemotherapy on cognitive and brain functions, thereby improving quality of

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life of cancer survivors.

The past two decades have seen a surge of interest in using neuroimaging techniques in an effort to better understand the impact of chemotherapy on cognitive functions. In one of the earlier studies in this area, Silverman et al. (2007) measured regional cerebral blood flow and metabolism using positron emission tomography (PET) in Chemo+ between 5–10 years after treatment and compared them with age-matched controls. PET scans were acquired at rest and while participants performed a verbal word recall memory task. Despite equivalent performance, compared to controls, the Chemo+ group showed increased cerebral blood flow in the inferior frontal gyrus during the word recall task. The enhanced activity for comparable task performance suggested a compensatory mechanism and/or greater effort or allocation of resources dedicated to the task.

Subsequent fMRI studies have, however, yielded equivocal results, with studies reporting both greater and lower activation in Chemo+ compared to controls. For instance, Kesler et al. (2009) observed that Chemo+ breast cancer survivors had lower activation during encoding of visually presented words in left superior frontal gyrus relative to age-matched controls whereas those same survivors had enhanced activation during memory recall of the words in the right superior temporal gyrus extending into inferior and medial temporal lobe. De Ruiter et al. (2011) compared the brain activity of Chemo+ patients and controls while performing the Tower of London and a paired associates task. Results in that study showed greater activation in patients than controls in left parietal operculum during both tasks. However, Chemo+ patients had less activation than controls in brain areas important for attention and memory, including dorsolateral prefrontal cortex, bilateral posterior parietal cortex, and parahippocampal gyrus. Menning et al. (2017) found greater activation in Chemo+ than Chemo– patients in bilateral inferior parietal cortex extending to superior parietal cortex, with the Chemo– showing significantly lower activation than healthy controls in inferior parietal cortices. This finding is inconsistent with results from other studies showing decreased activation in Chemo+ relative to either age-matched controls (e.g., Conroy et al., 2013; Correa et al., 2017; Deprez et al., 2014; Kam et al., 2016a; Lopez Zunini et al., 2013; McDonald et al., 2012; Wang et al., 2016) or Chemo– (e.g., de Ruiter et al., 2011; Kesler et al., 2011; Vardy et al., 2019). The treatment-related hypo-activation observed in these fMRI studies may be indicative of a more fundamental difference between Chemo+ and Chemo– in ability to mobilize and engage attentional resources. This would be consistent with Chemo+ patients' reports of mental fatigue; their attentional resources, in a sense, may be depleted which in turn results in difficulties in allocating and maintaining attention to the task at hand (Selamat et al., 2014; Shilling and Jenkins, 2007).

The current meta-analysis combines results across fMRI studies to quantify common brain areas and activation patterns that differentiate Chemo+ from cancer patients who did not receive chemo or non-cancer controls, across cancer types and cognitive tasks. We chose to focus on fMRI studies using a task-based paradigm because of the similarity between the experimental tasks and some of the neuropsychological assessment used to quantify CRCD. While there is an increased number of resting-state (rs) fMRI studies, the findings from these studies are difficult to relate to CRCD because of the lack of any goal directed task. Moreover, the approaches to analyzing rs-fMRI are more variable and often concentrate on pre-determined region(s) of interest rather than whole brain activation.

We used Activation Likelihood Estimation (ALE) software to analyze activation results from relevant fMRI and PET studies (Eickhoff et al., 2012, 2009; Turkeltaub et al., 2012). The ALE statistic describes the voxel-wise likelihood of activation from published neuroimaging studies and provides a means of identifying brain regions that are reliably recruited across multiple studies and/or in different laboratories. The present meta-analysis may also inform two fundamentally different accounts of CRCD. According to the compensatory hypothesis, we should observe enhanced activity in a cluster of brain areas in Chemo+. In contrast, if chemotherapy impacts the ability to mobilize and engage attentional resources then we would expect to observe lower brain activation in Chemo+.

2. Materials and methods

2.1. Search strategy

Search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The PubMed (www.pubmed.org) database was searched using combinations of the following terms: "cancer", "neoplasm", "memory", "working memory", "chemo", "chemotherapy", "chemo-brain", "systemic therapy", "fMRI", "cognition" and "neuroimaging". The references of all relevant review papers retrieved in the primary search were then hand-searched for articles not previously identified. The search included articles published in peer-reviewed journals and in English as of August 2020. The Pubmed search yielded 669 results. References of all relevant articles were then searched for potentially eligible articles. See Supplementary material for complete search strategy.

2.2. Screening process

Each article was screened based on its title and abstract against eligibility exclusion criteria outlined in Fig. 1. Full texts of potentially eligible articles were retrieved and screened, and any disagreements were settled by consensus among authors.

Articles were included if the study or studies described met the following criteria: (1) included a behavioral task performed during scanning; (2) included a control experimental condition; (3) conducted whole brain analysis from fMRI or PET and reported 3D coordinates in either Talairach (Talairach and Tournoux, 1988) or Montreal Neurological Institute (MNI) standardized space; (4) included participants who were diagnosed with a non-CNS cancer and had received chemotherapy.

In the sample of studies that met the inclusion criteria, two studies did not report behavioral data from the task used during scanning (Table 1). Moreover in two other articles, the effect of chemotherapy on brain activation was assessed using two different tasks (de Ruiter et al., 2011; Stouten-Kemperman et al., 2015) and the contrasts and resulting coordinates associated with the different tasks were reported separately. In those instances, coordinates from both tasks were included in the meta-analyses. One article provided both within (i.e., longitudinal) and between-subject (i.e., cross sectional) comparisons for the same task (McDonald et al., 2012), and both sets of coordinates were included, with the corresponding number of participants for the within and the between group contrasts.

2.3. Activation likelihood estimate (ALE)

Coordinate-based quantitative meta-analyses of neuroimaging results were performed using the GingerALE software (version 3.02) available on the BrainMap website (http://brainmap.org/ale/index.html). The Talairach coordinates were converted to MNI space using the Lancaster transformation (Lancaster et al., 2007) before being entered into the analysis. This software generates a brain activation map based on coordinates provided in the included articles and uses a permutation test to determine whether the group mean activation is statistically reliable or not. The GingerAle software creates probability maps, where probabilities are modeled using a three-dimensional Gaussian density distribution centered on each coordinate reported in an experiment. For each Gaussian probability distribution function, the full-width half-max (FWHM) is weighted by the number of participants included in the experiment, such that experiments with a larger sample size will have a tighter and taller Gaussian, thereby providing a better

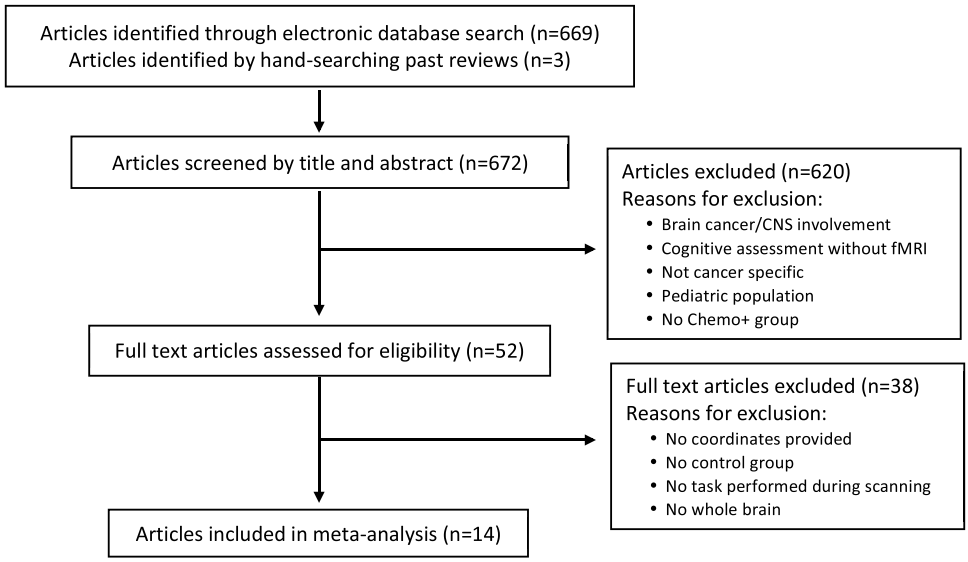

Fig. 1. PRISMA Diagram depicting screening process for studies included in meta-analysis.

estimate of true activation. The FWHM is first estimated using the Euclidian distance between foci representing the spatial uncertainty around each coordinate. Next the software calculates combined probabilities of activation for each voxel. Finally, voxel-wise scores are yielded, indicating convergence of activation in similar brain locations across studies (i.e., activation cluster). Foci that lie outside an activation cluster contribute to ALE clusters, but their contribution to the activation cluster diminishes as a function of distance from the maximum of overlap between Gaussian distributions.

We used the smaller mask size and the random effect Turkeltaub Non-Additive method, which minimizes both within-experiment and within-group effects by limiting probability values of neighboring foci from the same experiment (Turkeltaub et al., 2012). In order to account for the possibility of false negatives introduced by the low number of studies included, we used single study P-value thresholding to detect brain regions consistently activated in Chemo+. This method set any voxel where the P value image had a value over the threshold to zero. To counter this liberal method, we also used the recommended conservative threshold of $p < .001$. The minimum volume was set to 500 mm^3. Coordinates were selected for inclusion if they reflected: (i) activations from a direct comparison between Chemo+ patients and Chemo– or non-cancer controls; or (2) activations from the same participants before and after chemotherapy.

In order to visualize the results, we used the program Mango (v.4.1), available on BrainMap (http://brainmap.org/ale/index.html). The ALE-statistic maps were overlaid on a MNI space template (Colin27_T1_seg_MNI.nii). For visualization, BrainNet software was used to display foci (Xia et al., 2013).

3. Results

Search results are shown in the PRISMA Flow diagram shown in Fig. 1.

Our objective was to identify brain areas that show consistently higher or lower activation in Chemo+. Fourteen articles met inclusion criteria and details of these studies are included in Table 1, and together comprise 375 Chemo+ and 429 non-cancer and chemotherapy-naïve cancer controls. Of those, ten articles reported lower task-related activation in patients who received chemotherapy and no hyperactivation. Three articles reported both enhanced and decreased activation in Chemo+. Only one article reported enhanced activation in Chemo+ but no hypoactivation. In total, 20 contrasts yielded the foci included in the analysis. Eight studies reported no difference in performance between Chemo+ and controls while four studies observed lower performance in Chemo+ than controls. Two studies did not report performance during the fMRI task.

Fig. 2 shows the distribution of all of the individual foci from the 20 contrasts used in the meta-analyses for studies showing chemotherapy-related changes in brain activation. From articles reporting any enhanced activation in Chemo+, the total number of foci was 15 and the total number of participants was 173. The ALE meta-analysis of these data did not yield any significant cluster. From studies reporting any lower activation in Chemo+, the total number of foci was 86 and the total number of participants was 760 (Table 1). The ALE statistic yielded two significant clusters.

The first cluster had four peaks in the left hemisphere, and the cluster was primarily located in the superior parietal lobule (59 %), extending into precuneus (22.5 %), inferior parietal lobule (16.2 %), and angular gyrus (1.6 %). There was six experiments that had at least one foci within the activation cluster. The experimental tasks showing foci within the cluster included the Tower of London (de Ruiter et al., 2011; Stouten-Kemperman et al., 2015), paired associates (de Ruiter et al., 2011; Stouten-Kemperman et al., 2015), and visual n-back tasks (Correa et al., 2017).

The second cluster had a single peak in the right hemisphere and was primarily located in the right precentral gyrus (69.2 %), extending into the right inferior frontal gyrus (30.8 %). The experimental tasks showing foci within the cluster were Stroop (Kam et al., 2016a), and visual n-back tasks (Vardy et al., 2019). The coordinates of the cluster-level brain areas consistently different between the groups are shown in Table 2. Fig. 3 displays the ALE-statistic maps for regions of statistically significant concordance.

4. Discussion

This meta-analysis of fMRI studies identified the brain areas showing consistent functional changes across cognitive tasks in non-CNS cancer survivors treated with chemotherapy. The ALE statistic of brain coordinates from fMRI studies yielded two significant clusters and both of them showed lower activation in cancer patients who had received chemotherapy as compared with patients who had not received chemotherapy or healthy age-matched controls. One of the clusters was located in the left superior and inferior parietal area and the second cluster was in the right superior prefrontal cortex, extending to inferior frontal gyrus. In both areas, the reduced activation was observed independently of behavioral findings.

Table 1
Studies included in the meta-analyses.

Study	Groups	Age in years, Mean ± SD, (Range)	Chemo description	Time since chemo	Task description & Behavioural Results	fMRI Contrast	Foci	Coordinate Space	Source of Coordinates
Conroy et al., 2013	BC post chemo (BC+, n = 24); Healthy control (HC, n = 23)	BC+: 57.8 ± 9.6 (41–78) HC: 61.2 ± 2.3 (46–79)	AC; AC-T; CAF; A–T; CMF; CMF + CAF; T; AC-T + cap or + taxane & cap	Mn 6.4 yrs	Verbal N-Back BC+ vs. HC, ns	BC+ < HC BC+ > HC	2 0	MNI	Table 2
Correa et al., 2017	Ovarian post chemo (OC+, n = 18); Healthy control (HC, n = 18);	OC+: 56.1 ± 8.2 (39–69) HC: 56.2 ± 9.1 (35–67)	taxane and platinum-based chemo	Range 1–4 mos	Visual N-Back OC+ vs. HC, ns	OC+ < HC OC+ > HC	8 0	MNI	Table 3
de Ruiter et al., 2011	BC post chemo (BC+ n = 19); BC no chemo (BC–, n = 15)	BC+: 56.3 ± 5.5, BC–: 58.2 ± 5.8 Range not reported.	FEC + CTC	Mn 9.5 yrs	Tower of London BC+ < BC– Paired Associates BC+ < BC–	BC+ < BC– BC+ > BC– BC+ < BC– BC+ > BC–	4 0 8 1	MNI Table 3	Table 2 Table 3
Deprez et al., 2014	BC pre & post chemo (BC+, n = 18); BC pts no chemo (BC–, (n = 16); Healthy control (HC, n = 17)	BC+: 43.7 ± 4.3 BC–: 44.3 ± 4.7 HC: 40.8 ± 6.0 Range not reported.	FEC; FEC + pac	Mn 173 days	Multitask paradigm: Visual & auditory n-back + short-term visual memory; BC+ vs. BC– vs HC, ns	BC+: T1 > T2	2	MNI	Table 3
Kam et al., 2016a	BC post chemo (BC+, n = 12); Healthy Controls (HC, n = 12)	BC+: 52.1 ± 5.4 (40–65) HC: 59.3 ± 4.1 (40–65)	AC; DC; FECD	Mn 11 mos	Stroop Task BC+ vs HC, ns	BC+ < HC BC+ > HC	17 0	Talairach	Table 3
Kesler et al., 2009	BC post chemo (BC+, n = 14); Healthy Controls (HC, n = 14)	BC+: 55.1 ± 8.0 (43–65) HC: 54.2 ± 8.0 (40–65)	CMF; ACT	Mn 3.3 yrs	Verbal Encoding Accuracy & Reaction Time (RT): ns Verbal Recall Accuracy: ns RT: BC+ >HC	BC+ < HC BC+ > HC BC+ < HC BC+ > HC	1 0 0 1	MNI	Table 2 Table 3
Kesler et al., 2011	BC post chemo (BC+, n = 25); BC no chemo (BC–, n = 19); Health controls (HC, n = 18)	BC+ = 56.2 ± 7.8, BC– = 58.1 ± 6.5, HC = 55.6 ± 9.4 Range not reported.	AC-pac or D; AC; Carb + D; C + pac or D; DCEF; CMF; ACF	Mn 4.7 yrs	Card Sorting BC+ < HC and BC–	BC+ < HC BC+ > HC or BC–	3 0	MNI	Table 3
Lopez Zunini et al., 2013	BC pre and post chemo (BC+ n = 21); Healthy controls (HCs, n = 21)	BC+: 50.6 ± 8.4 (35–64) HC: 49.6 ± 8.7 (31–61)	FECD; FECD + hepirubicin; DC; AC	Mn 31 days	Verbal memory recall BC+ vs HC, ns	BC+ T2 < T1 BC+ T2 > T1 BC+ < HC at T2 BC+ > HC at T2	4 0 4 0	MNI	Table 6
McDonald et al., 2012	BC pre & post chemo (BC+ n = 16); BC no chemo (BC–, n = 12); Health control (HC, n = 15)	BC+: 52.9 ± 8.6 BC–: 52.7 ± 7.2 HC: 50.5 ± 6.0 Range not reported.	AC-pac; AC-doce; AC	Pre CT; 1 mo post CT 1 yr post CT	N-Back BC+ vs. BC– vs. HC, ns at any time points	BC+ < HC at T2 BC+ > HC at T2 BC+ < BC– at T2 BC+ > BC– at T2 BC+ < HC at T3 BC+ > HC at T3 BC+ < BC– at T3 BC+ > BC– at T3 BC+ T2 < T1	1 0 0 0 1 1 0 3 3	MNI	Table 2

(*continued on next page*)

Table 1 (*continued*)

Study	Groups	Age in years, Mean ± SD, (Range)	Chemo description	Time since chemo	Task description & Behavioural Results	fMRI Contrast	Foci	Coordinate Space	Source of Coordinates
Menning et al., 2017	BC pre and post chemo (BC+, n = 28); BC no chemo (BC–, n = 24); Healthy controls (HC, n = 31)	BC+: 49.4 ± 8.8 BC–: 51.2 ± 6.8 HC: 51.2 ± 8.2	AC; AC-D; AC-pac; FEC	Mn 201 days	Tower of London No differences.	BC+ > BC– at T2 (T1 adjusted) BC+ < BC– at T2	9 0	MNI	Table 3
		Range not reported.			Paired associates No differences.	All contrasts	0		
Stouten-Kemperman et al., 2018	Testicular post chemo (TC+, n = 28); Testicular no chemo (TC–, n = 23)	TC+: 43.1 ± 7.5 TC–: 48.2 ± 9.5 Range not reported.	BEP	Mn 14.7 yrs	Emotional Face Match Performance not reported	TC+ < TC– TC+ > TC–	6 0	MNI	Table 2
Stouten-Kemperman et al., 2015	BC post high dose chemo (BC+Hi, n = 17); BC post standard chemo (BC+S, n = 24); BC no chemo (BC–, n = 15); Healthy controls (HC, n = 27)	BC+Hi: 56.3 ± 5.5 BC+S: 59.8 ± 6.3 BC–: 58.2 ± 5.8 HC: 60.31 ± 4.8 Range not reported.	BC+S: FEC; BC+Hi: FEC + A-Thio-carb	BC+Hi: 9.5 yrs BC+S: 13.4 yrs	Tower of London BC+Hi < BC– BC+Hi < BC– BC+S < BC–	BC+Hi < BC– BC+Hi > BC– BC+S < BC– BC+S > BC–	2 0 2 0	MNI	Table 3
					Paired Associates BC+Hi > BC+S BC– > BC+S BC– >HC	BC+Hi < BC– BC+Hi > BC– BC+S < BC– BC+S > BC–	7 0 6 0		
Vardy et al. 2017	BC post chemo with cognitive symptoms (BC+ CS+, n = 44); BC post chemo without cognitive symptoms (BC+ CS-, n = 52); BC no chemo (BC–, n = 30);	BC+ CS+: Median = 48.4 (30−60) BC+ CS–: Median = 48.4 (29−60) BC–: Median = 54.1 (30−59)	not provided	< 5 yrs	Visual N-Back Performance not reported	BC+ < BC– BC+ > BC–	6 0	MNI	Supp. 1
Wang et al., 2016	Mixed cancers post chemo (Ch+, n = 15); Healthy controls (HC, n = 14)	Ch+: 50.7 ± 7.5; HC: 53.0 ± 7.2 Range not reported.	not provided	< 6 mos	Visual N-Back Ch+ vs HC, ns	Ch+ < HC Ch+ > HC	1 0	Talairach	Table 5

Notes.
Mn- mean; Yrs- years; mo- month; BC- breast cancer.
C- cyclophosphamide; M- methotrexate; F- 5-fluorouracil; A- adriamycin (doxorubicin); E- epirubicin.
FEC + CTC: 5-fluorouracil, epirubicin, cyclophosphamide + cyclophosphamide, thiotepa, carboplatin.
FEC(D)- 5-Flourouracil, Epirubicin, Cyclophosphamide, (docetaxel).
AC- Doxorubicin + Cyclophosphamide; DC - Docetaxel + Cyclophosphamide; ACT- adriamycin, cyclophosphamide, taxol/taxotere.
BEP- bleomycin; etoposide; cisplatin.
D- docetaxel; Pac- paclitaxel; carb- carboplantin; cap- capecitabine; thio- Thiotepa.
The last column (i.e., Source) indicates where in the published article the coordinates are presented.

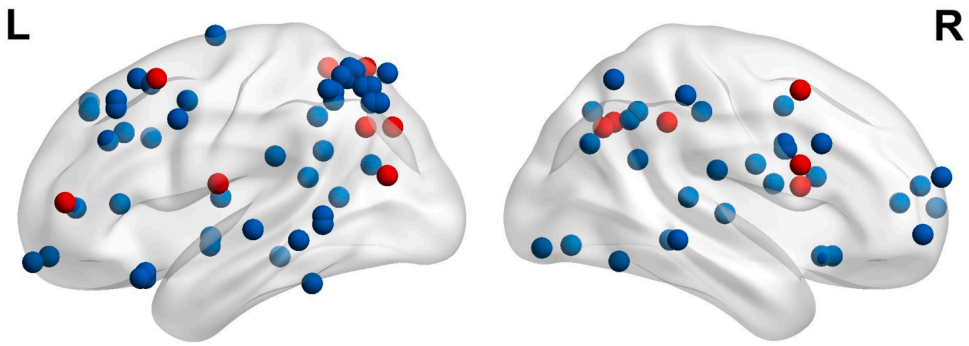

Fig. 2. Foci from studies showing greater activation (Red) and from studies reporting lower activation (Blue) associated with chemotherapy. L = Left; R = Right.

Table 2
A list of significant clusters generated from the meta-analysis.

Cluster #	Lobe, Brodmann Area	MNI coordinate of cluster center (x,y,z)	Cluster size (mm^3)	#Studies/ Cluster
1	Left Parietal Lobe, BA 7	−32.9,-61.8,52.2	2520	6
2	Right Frontal Lobe, BA 6	51.6,4.4,28.4	520	2

Note: The statistical analysis was computed on coordinates from 20 contrasts showing hypoactivation in between Chemo+ versus healthy controls or within the same participants after (Chemo+ versus prior to treatment (Chemo–). The number of studies per cluster correspond to a list of studies with foci within the cluster's boundary. Foci that lie outside a cluster do contribute to an ALE cluster, but the magnitude of the contributing effect drops as a function of distance from the maximum of overlap between Gaussian distributions.

4.1. Hypoactivity and functional abnormalities in attention and executive processes

The left superior parietal area is part of the fronto-parietal attention network (Mesulam, 1999). Evidence indicates that this network is critical for attentional regulation (Behrmann et al., 2004; Han et al., 2004) and plays an important role in memory retrieval (Ciaramelli et al., 2008) and memory-guided attention (Fischer et al., 2020; Goldfarb et al., 2016; Summerfield et al., 2006; Zimmermann et al., 2020). Lower activation in this network in Chemo+ may reflect anomalies in allocating attention, which could result in difficulties across cognitive tasks. Difficulties in focusing attention on the task at hand is consistent with patients' subjective reports and would contribute to individual differences in the types of cognitive complaints reported by cancer patients treated with chemotherapy. An alternative (albeit not mutually exclusive) possibility is that CRCD is primarily related to decreased attentional resources such that patients treated with chemotherapy are less able to successfully recruit brain areas important for engaging in tasks (e.g., frontal-parietal attention network). This would help explain why patients report problems in such a diverse assortment of domains. Lastly, activation in superior parietal cortex (area BA7) has been associated with various movements, including grasping and reaching (Le et al., 2017), and is thought to plays a role in stimulus response mapping by indexing efficiency in target-response associations (Randerath et al., 2017). Hence, it is also possible that the hypoactivation in this area reflects a disruption in visuo-motor coordination, and would explain why it was seen in left hemisphere given that most participants responded using their right hand.

Hypoactivation in the right superior prefrontal cortex is also consistent with involvement of an extended frontoparietal control network (Matsuo et al., 2003). Activation in the right precentral and inferior frontal gyrus has been associated with working memory (e.g., Gillis et al., 2016), visual short-term memory (e.g., Koyama et al., 2011), interference control and fluid intelligence (Burgess and Braver, 2010; Burgess et al., 2011), as well as resource sharing in working memory tasks (Vergauwe et al., 2015). These areas have also been shown to contribute to attention and memory by interfacing long-term memory representations with external incoming information during visual search (Leech and Sharp, 2014; Rosen et al., 2018). The ALE statistic maps suggest that chemotherapy may impact areas needed to support attentional regulation and executive control functions across several different cognitive tasks. The present meta-analysis did not yield reliable pattern of chemo-related de-activation in the anterior prefrontal cortex. This was somewhat surprising given the tasks used in fMRI studies assessing the impact of chemotherapy on cognitive functions (e.g., n-back, Stroop). One possible explanation is that areas within the anterior prefrontal cortex are more task dependent, hence would be less likely to show significance with ALE because the foci came from a variety of tasks. Additional CRCD fMRI studies may enable a more refined (task--specific) examination of the brain network impacted by chemotherapy.

Hypoactivation in parietal and prefrontal cortices is associated with lower performance on attention tasks and has been shown to be related to cognitive fatigue (Lim et al., 2010), and attention deficit disorders (Bush, 2011). Moreover, patients with rheumatoid arthritis who often suffer from chronic fatigue show enhanced functional connectivity in the dorsal attention network and increased grey matter volume in putamen (Basu et al., 2019). Using positron emission tomography, Hosp et al. (2021) showed frontoparietal hypometabolism in patients hospitalized with acute respiratory syndrome coronavirus disease-19. The hypoactivation observed in these studies suggests that chemotherapy may be associated with difficulties allocating and maintaining attentional resources, which in turn could lead to more variable performance in cognitive tasks.

The parietal and frontal areas observed in the present meta-analysis are part of the dorsal stream, which plays an important role in on-line motor control (Alain et al., 2010; Dressing et al., 2020; Sakreida et al., 2016). Therefore, it is possible that the hypoactivation observed in superior prefrontal and parietal cortices could index psychomotor retardation, which refers to slowing down of thought and action (Walther et al., 2012; Yin et al., 2018). This could help explain findings showing that Chemo+ have more intra-individual variability (IIV) than age-matched healthy and non-chemo controls (Bernstein et al., 2014; Collins et al., 2018; Yao et al., 2017b). Research has linked IIV with deficits in attention, with IIV representing inconsistent neuronal transmission in parietal-frontal networks important in sustained attention and working memory (Russell et al., 2006) and others who argue that IIV may reflect a disintegration of white matter in parietal and frontal lobes (Costa et al., 2019; MacDonald et al., 2006). Importantly, our results, along with those from other clinical populations suggest that hypoactivation may not be necessarily specific to chemotherapy, but may represent a more general condition that follows a stressful event that may deplete brain or cognitive reserve, including neural reserve and/or neural compensation (Stern, 2009, 2013).

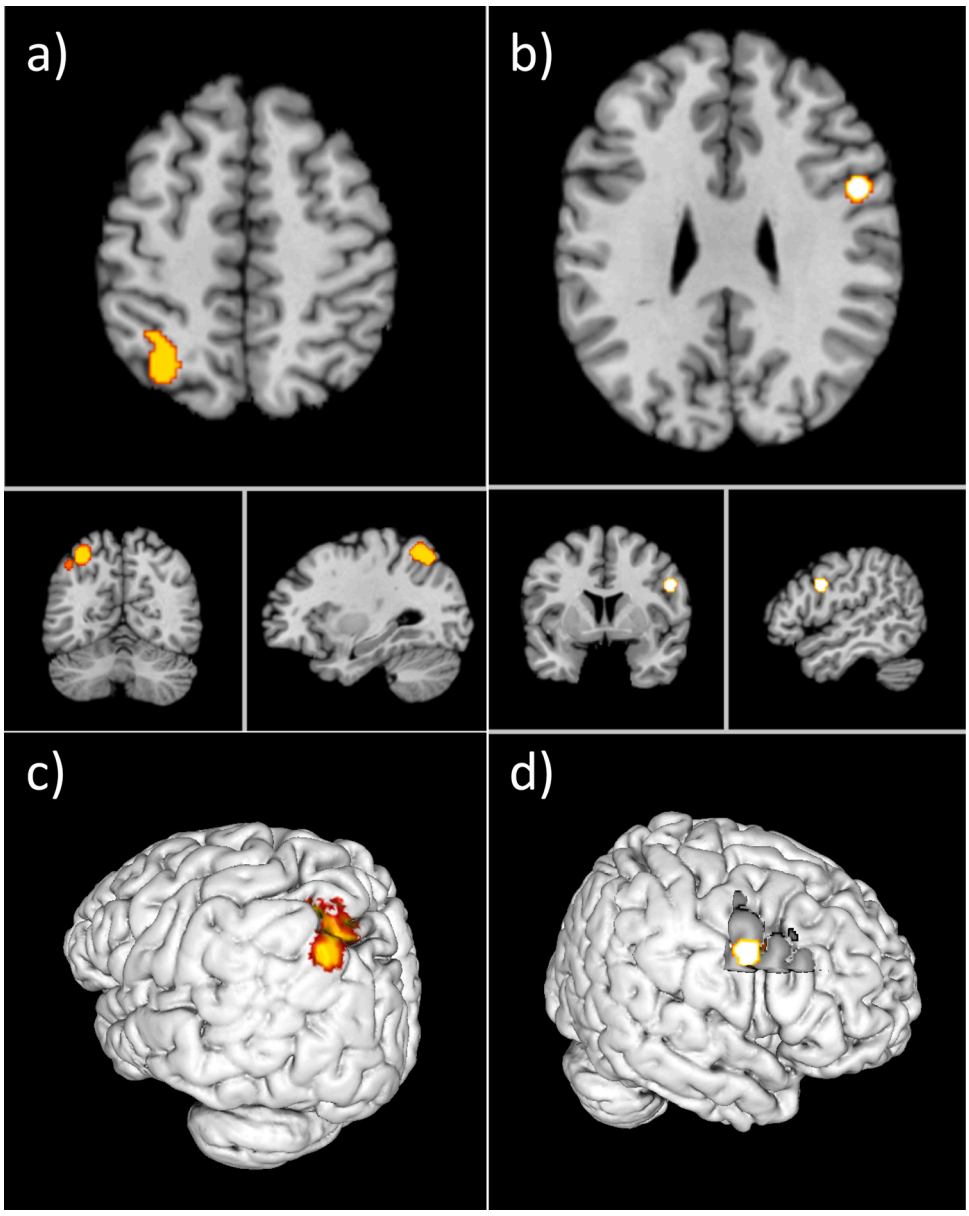

Fig. 3. ALE-statistic maps for regions of significant concordance in neuroimaging studies reporting lower brain activity in Chemo+ than in healthy controls or within the same participants after (Chemo+ versus prior to treatment (Chemo–). a) Axial, coronal and sagital views of the first cluster from ALE statistic. b) Axial, coronal and sagital views of the second cluster. c) 3-D brain showing the first cluster. d) 3-D brain showing the second cluster.

The hypoactivation in parietal and prefrontal cortex may also explain the effects of chemotherapy on electrophysiological measures of attention. For instance, one consistent finding is that of a reduced P3b amplitude, and a change in latency that appears to be related to having chemotherapy (Kam et al., 2016b; Kreukels et al., 2005, 2008; Schagen et al., 2001). The P3b is a cognitive ERP component, associated with working memory updating (Kirschner et al., 2015; Picton, 1992). The P3b peaks about 300−600 ms after target onset and receives contributions from a widely distributed network of brain regions including the medial temporal lobe, the parietal cortex, and the prefrontal cortex (Alain et al., 1989; Baudena et al., 1995; Halgren et al., 1995a; Picton, 1992; Polich, 2007). Prefrontal and parietal lesions have both been associated with reduced P3b amplitude (Knight et al., 1989; Lovstad et al., 2012; Yamaguchi and Knight, 1991). Moreover studies using transcranial magnetic stimulation have shown that repetitive stimulation over the prefrontal and parietal cortices modulate the amplitude and latency of the P3b ERP component, providing strong support for the role of the parietal cortex on P3b generation (Capotosto et al., 2012; Evers et al., 2001; Hill et al., 2019).

4.2. *Hypoactivity reflects structural abnormalities in these areas after chemotherapy*

The reduced parietal activation in Chemo+ may be attributable to chemotherapy-related brain structural alterations. In a prospective study, Brown et al. (1998) showed a rapid and progressive accumulation of white matter changes in a small sample of patients up to about six month after chemotherapy, which then stabilized. Subsequent studies have replicated these alterations in white matter in cancer survivors (Blommaert et al., 2019; Kesler et al., 2015), indicating that chemotherapy disrupts network connectivity supporting cognitive processes. Deprez et al. (2011) also found that in breast cancer survivors, chemotherapy was associated with widespread reductions of white matter integrity in the cingulum and superior frontal occipital fasciculus, regions connected with default mode network regions.

In addition to changes in white matter, evidence suggests that

Chemo+ patients also show greater changes in grey matter density than age-matched controls (Amidi and Wu, 2019). For instance, Inagaki et al. (2007) found reduced gray matter density in prefrontal, parahippocampal gyrus and precuneus in patients who received chemotherapy for breast cancer compared with those who did not. The volume in the superior frontal gyrus correlated with measures of attention/-concentration and visual memory. The difference in brain volume between patients who received and those who did not receive chemotherapy was present one year after treatment. No such difference between groups was found three years after treatment. Subsequent studies have revealed reduced gray matter density in breast cancer Chemo+ survivors in prefrontal (Li et al., 2018; McDonald et al., 2013; Zou et al., 2017), temporal (Zou et al., 2017), parietal (de Ruiter et al., 2012; Zou et al., 2017), occipital (de Ruiter et al., 2012) and cerebellar regions (de Ruiter et al., 2012; Li et al., 2018). Together, these findings suggest some persistent effects of chemotherapy on brain structure that may parallel some of the previous reports from neuropsychological studies.

4.3. Resting state fMRI

This meta-analysis did not include results from studies measuring resting-state brain activity in Chemo+ cancer survivors because most of the resting-state studies used region of interest rather than the whole-brain approach (e.g., Bruno et al., 2012; Chen et al., 2020; Cheng et al., 2017; Kesler et al., 2017). Furthermore, of those studies that did assess the whole brain, only a subset of those studies reported coordinates (e.g., Chen et al., 2019; Kim et al., 2017; Mo et al., 2017; You et al., 2020).

Results from the resting-state fMRI studies appear inconsistent, with some studies reporting increased resting-state activity in the same brain areas that other studies report a decrease. Mo et al. (2017) found Chemo+ had enhanced resting-state activity in right orbitofrontal, right middle and superior temporal gyrus, and left dorsolateral prefrontal cortex and reduced resting-state activity in anterior and posterior cerebellum. Shen et al. (2019) similarly found Chemo+ had enhanced resting-state activity in prefrontal and parietal cortices while Chen et al. (2019) observed that Chemo+ increase rs-activity in right subcallosal gyrus and right anterior cingulate. The reasons for this increased resting state activity is unclear, but could reflect default mode network abnormalities, which is associated with mind wandering (Gruberger et al., 2011). However, other studies have shown opposite patterns in some of these same brain areas, with results indicating Chemo+ having lower resting-state activity in prefrontal cortex (Kim et al., 2017; You et al., 2020), parietal cortex (You et al., 2020), precuneus (Chen et al., 2019), bilateral middle temporal gyrus, right inferior temporal gyrus, right angular gyrus and left insula (e.g., Chen et al., 2020). Bai et al. (2021) also found reduced activity in left prefrontal cortex (BA 9) and right mid temporal areas (BA 22) after chemotherapy.

In summary, findings from resting-state studies to date are inconsistent with one another. The discrepancy in the resting-state literature could be related to methodological differences used to assess and interpret resting-state fMRI. Future advances in understanding the impact of chemotherapy on resting-state fMRI would benefit from studies using comparable experimental designs and statistical analyses in order identify common patterns of default mode networks in cancer patients previously treated with chemotherapy (Deprez et al., 2018).

4.4. Functional connectivity during either resting state fMRI or task-related fMRI

There is a growing interest in assessing whether, and if so, how chemotherapy affects functional connectivity among brain regions needed for perceptual, sensorimotor, and cognitive functions. While functional connectivity analyses in cancer patients treated with chemotherapy has been shown to include areas consistent in attention networks, the directionality (and possible areas) are not consistent across studies. For instance, using an n-back task, Dumas et al. (2013) showed decreased functional connectivity in the dorsal attention network one month after chemotherapy that had partially returned to baseline one year later. In other cases, greater connectivity was reported, with higher task-related hippocampal-cortical connectivity (left cuneus, left lingual, left precuneus, and right middle prefrontal gyri) in Chemo+ (Apple et al., 2018). Notably, the findings from these functional connectivity studies revealed Chemo+ alteration in connectivity including brain areas identified in the present meta-analysis such as the left parietal cortex and left precuneus.

Bruno et al. (2012) examined large-scale brain networks during resting-state fMRI using graph theory. Chemo+ was associated with a disruption of a global brain network as well as altered regional networks in bilateral frontal, striatal and temporal areas, and these results are relatively consistent with results from our meta-analysis. Wang et al. (2016) assessed resting-state functional connectivity using the right dorsolateral prefrontal cortex as a seed. That study reported decreases in functional connectivity in Chemo+ compared to age-matched controls in the left superior temporal gyrus, right inferior frontal gyrus, and right medial frontal gyrus. In a more recent study, Zhang et al. (2020) examined the intrinsic functional connectivity pattern within the default mode network and its associations with cognitive impairment in patients with lung cancer. The posterior cingulate cortex was chosen as the seed region to detect the functional connectivity patterns and then determine whether these changes were related to cognitive performance. Compared with Chemo– patients, Chemo+ had decreased functional connectivity between the posterior cingulate cortex and the right anterior cingulate cortex, left inferior parietal lobule, and left medial prefrontal cortex, as well as increased functional connectivity with the left postcentral gyrus. Relative to healthy controls, Chemo+ patients exhibited reduced functional connectivity between the posterior cingulate cortex and the left anterior cingulate cortex and left temporal lobe, as well as increased functional connectivity with the right postcentral gyrus.

Feng et al. (2020) used a prospective study design to assess the impact of chemotherapy on nine different resting-state brain networks: default mode network (DMN), frontoparietal network (FPN), dorsal attention network, (DAN), sensorimotor network (SMN), central executive network (CEN), self-referential network (SRN), visual network (VN), auditory network (AN), and central network (CN). The within-network and between-network functional connectivity did not significantly differ among cancer patients and controls (for a different finding see Bromis et al., 2017). In an analysis focusing on cancer patients only, Feng et al. found increased within-network functional connectivity one week after chemotherapy treatment in several networks (e.g., DMN, PDMN, LFPN, RFPN, SRN and CN), which then decreased to match that of within-network connectivity prior to treatment. The findings from this study suggest a short-lived effect of chemotherapy on brain functional connectivity.

Overall, functional connectivity analyses using tasks or resting-state fMRI data suggest a distribution in connectivity between prefrontal cortices and posterior brain region including the parietal cortex. Reduced functional connectivity between prefrontal cortex and posterior regions could play a role in the observed hypoactivation in prefrontal and parietal cortex that our meta-analysis showed.

5. Limitations and recommendations

Meta-analyses of neuroimaging studies enable identification of core brain regions that support task performance independent of differences in methodology (e.g., sample size, materials used, scanner type). The ALE coordinate-based meta-analytic method provides a measure of activation location consistency. However, it does not provide an effect size of the ALE statistic map, which would be useful for further clinical investigations. Moreover, one needs to consider the number of studies,

types of studies, as well as methodology and statistical thresholds used. We adhered to recent guidelines for meta-analyses using ALE software (Eickhoff et al., 2012). The number of studies included in each meta-analysis was sufficient to yield reliable patterns of activation. It is possible that these patterns of activation may change as more studies are published. A compensatory account of CRCD predicts hyperactivity, but not necessarily to occur in a common location because the areas "recruited" may be more task-specific. It is possible that we did not find significant common areas of hyperactivation because the tasks differed across studies. An account that posits that CRCD is a failure of engagement of attentional resources, however, predicts hypoactivation in areas common for mobilization of attentional resources across tasks, which include frontal parietal areas. Because insufficient numbers of resting state amplitude of low frequency fluctuations (ALFF) or arterial spin labeling (ASL) studies comparing Chemo+ to a comparison group have been published to date, we did not include these in the quantitative meta-analysis.

Some recommendations to further advance understanding the neural basis of CRCD should be considered:

1 As previously recommended by the International Cognition and Cancer Task Force (Deprez et al., 2018), articles should report detailed coordinates for both hypo and hyper-activation, and for which specific tasks.
2 The two cluster areas found to be significant across all studies to date, regardless of what cognitive task was being done, should be included in future structural and functional studies using an ROI approach or as seeds in functional connectivity studies.
3 As more studies are done that look at whole brain activity on Chemo+ and healthy age-matched or non-Chemo+ controls, future meta-analyses should assess the role of task performance in putative group differences in brain activation. For instance, fMRI studies could be segregated into those showing behavioral performance equivalence versus studies showing Chemo+ performing worse than the comparison cohort.
4 As more studies are published, fMRI studies could be grouped as a function of the time between treatment and the fMRI experiment to distinguishing between acute and long-term chemotherapy-related cognitive effects on cancer survivors.
5 Most neuroimaging studies included in the present meta-analysis were with cancer patients who received anthracycline-based chemotherapy. However, some studies included patients who received Taxanes and platinum-based therapies. While it is important to consider the putative differential impact of different chemo regimens, the number of studies using different regimens is too small for reliable coordinate-based meta-analysis. Future research is needed to examine the impact of different chemo regimen on CRCD and brain activity. Furthermore, dosing of such agents should also be reported, and tracked, as it is possible that there are dose-dependent effects on brain activity.
6 More studies investigating cancers that affect both males and females are needed in order to better understand potential sex differences.
7 Most studies to date have used visually presented material. Further research should also assess to what extent chemotherapy may impact auditory or multi-sensory processing as well as attention and memory for auditory stimuli. This will help determine whether CRCD is modality specific or affects all modalities.
8 Future meta-analyses could consider integrating findings from multiple imaging modalities such as electroencephalography (EEG). Prior studies have used the P3b, a component of the ERP that is a marker of attentional focus, to reveal how CRCD impacts perception and attention by modulating the allocation of attention and by regulating the flow of information through sensory cortices. These studies are particularly interesting because source modeling or neuroelectric brain activity (Bledowski et al., 2004; Maurits et al., 2005; Shen et al., 2018) as well as intracerebral recording (Alain et al., 1989; Baudena et al., 1995; Halgren et al., 1995a, b) and lesion studies (Knight et al., 1989; Lovstad et al., 2012; Yamaguchi and Knight, 1991) suggest generators located in medial temporal lobe, parietal and prefrontal cortices. These findings provide converging evidence for the link between dysregulation in attention control network and CRCD.

6. Concluding remarks

This review and meta-analysis of fMRI studies aimed to identify a common set of brain areas underlying CRCD. The findings suggest that hypoactivation in parietal and prefrontal areas that have been previously identified as part of the frontoparietal attention and control networks likely contributes to CRCD. It is possible that this hypoactivation in parietal and prefrontal cortex reflects deficits from a more general system, such as the multiple-demand system implicated in general executive control (Cabeza & Nyberg, 2000; Camilleri et al., 2018; Duncan, 2010).

Neuroimaging investigation of CRCD is a growing field. Future meta-analyses would benefit from a greater number of studies to further clarify the impact of chemotherapy on brain networks enabling cognition. We have also suggested methodological considerations that may help to advance our understanding of CRCD. We have proposed that CRCD can be viewed as a failure to recruit the fronto-parietal attention control network while performing cognitive tasks. Further elucidating the link between CRCD and brain networks enabling attention and memory and understanding the neurobiology of CRCD may facilitate the development of interventions in cancer survivors to prevent or mitigate it.

Author contributions

LJB, KE, AS, and CA designed the study. LJB, CA, and AS were involved in data collection. CA analyzed the data. LJB, KE, AS, and CA interpreted data and wrote the manuscript.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.08.024.

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