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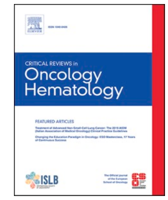

Evidence of brain-derived neurotrophic factor in ameliorating cancer-related cognitive impairment: A systematic review of human studies

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A B S T R A C T

Brain-derived neurotrophic factor (BDNF) plays an essential role in neurogenesis and neuroplasticity and may be a key protein in cancer-related cognitive impairment (CRCI). This systematic review assessed the relationship between BDNF biomarkers and neurocognitive outcomes in cancer patients and survivors. A search in PubMed, Scopus, and PsycINFO yielded 638 articles, of which 26 were eligible. Fourteen (54 %) studied BDNF protein levels while 15 (58 %) analyzed *BDNF* rs6265 polymorphism. Of the nine observational studies reporting BDNF plasma/serum levels, five (56 %) exhibited a positive association between BDNF and cognitive function. One study reported intra-tumoral BDNF levels that were negatively associated with memory. For rs6265, three (20 %) of 15 studies reported an association with cognitive function with inconsistent directions. Among seven neuroimaging studies, three (43 %) demonstrated an effect of BDNF on brain function and structure. These results suggest that BDNF is a potential monitoring biomarker and druggable target for CRCI.

1. Background

Cancer-related cognitive impairment (CRCI), often referred to as “chemobrain”, is prevalent in up to 75 % of all cancer survivors (Janelsins et al., 2018; Ng et al., 2018). CRCI encompasses a wide range of symptoms during and after treatment such as memory loss, inability to concentrate, difficulty in thinking, poor response speed, and executive functioning. Studies have reported cognitive changes can be subtle in cancer survivors; however, they may cause a detrimental effect on patients’ daily functioning and health-related quality of life (Ng et al., 2018; Cheung et al., 2012; Kobayashi et al., 2020). CRCI can also pose significant challenges for cancer survivors who wish to resume their day-to-day routine and social roles. Despite the debility caused by this condition, recommendations to prevent and treat CRCI are scarce. More research is required to improve the understanding of the pathogenesis underlying CRCI to innovate novel and effective interventions (Mayo et al., 2020).

There is growing evidence that brain-derived neurotrophic factor (BDNF) plays a significant role in cognitive health. Expressed by the *BDNF* gene, BDNF belongs to the neurotrophin superfamily and plays essential role in the neurogenesis and neuroplasticity of the brain. BDNF signaling, via tropomyosin receptor kinase B (TrkB) receptors, supports the survival of existing neurons and facilitates the proliferation and differentiation of new neurons and synaptic plasticity in both the central and peripheral nervous systems (Fig. 1) (Acheson et al., 1995; Huang and Reichardt, 2001). BDNF is extensively distributed within the central

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nervous system (CNS), highly expressed in the hippocampus, cortex, and basal forebrain, and has an important role in regions vital to learning and memory. In particular, BDNF's involvement in neurotransmitter release and long-term potentiation is important to learning and memory consolidation (Morris et al., 1986). Numerous studies have linked BDNF downregulation in the pathogenesis of cognitive disorders, such as Alzheimer's disease (AD), with low serum levels have been correlated with AD and mild cognitive impairment, and high serum BDNF levels (also known as mBDNF, Fig. 1) have been associated with better cognition in healthy older adults (Gunstad et al., 2008; Shimada et al., 2014; Teixeira et al., 2010; Zhang et al., 2012). Many factors, including age, degree of exercise and single nucleotide polymorphisms (SNPs) of the *BDNF* gene, may impact BDNF levels and subsequently cognitive performance, suggesting that BDNF is an important target for the study of cognitive health. While the downregulation of *BDNF* expression have yet to shown in CRCI-related preclinical studies, investigational therapeutics (e.g., stem cells and exosomes, (El-Derany and Noureldein, 2021) berberine, (Shaker et al., 2021) and resveratrol (Shi et al., 2018)) which ameliorated CRCI in animal models was also reported with enhanced BDNF levels.

Exposure to neurotoxins has been linked to long-term cognitive disturbances because of long-lasting reductions of BDNF mRNA levels in the brain (Onishchenko et al., 2008). Therefore, it is postulated that the neurotoxic effects of chemotherapy on BDNF expression can occur after the completion of chemotherapy and in cancer survivors, resulting in CRCI. However, it is currently unknown whether BDNF as a biomarker is associated with cognitive changes in cancer patients receiving chemotherapy and whether BDNF alone is an effective biomarker to evaluate the success of interventions for improving cognitive health in cancer patients. To evaluate whether BDNF is a potential monitoring and/or therapeutic target for CRCI, we conducted a systematic review to assess the association between BDNF biomarkers and cancer-related neurocognitive outcomes in the current literature.

2. Methods

2.1. Search Strategy

A literature search was conducted using PubMed, Scopus, and PsycINFO databases in March 2022. The search included articles published exclusively in English dated up to March 2022. Terms used for the search include the following: "BDNF", "brain derived neurotrophic factor", "cognition", "cognitive", "memory", "attention", "processing speed", "executive function", "multi-tasking", "neurocognitive", "neurocognition", "cancer", "carcinoma", "leukemia", "lymphoma", "tumor". Exclusion keywords included "mice", "mouse", "rat", "rats", "animal", and "animals". Index terms and MeSH terms were utilized where available.

2.2. Eligibility criteria

Published studies considered for this review included the following criteria: (1) inclusion at least one of the following neurocognitive outcomes: (i) subjective tests, self-reported cognitive abilities, (ii) objective tests, using a neuropsychological battery or by clinician assessment, or (iii) neuroimaging, involving the assessment of structural changes of brain function; (2) reporting of any BDNF biomarkers; (3) human studies. Excluded studies included animal research, in vitro, reviews, editorials, commentaries, and protocols. No restriction was placed on the number of patients for including the study.

2.3. Study screening

Two authors (DC and PA) performed title and abstract screening for each article, followed by all authors (DQN, DC, PA, and AC) performing a further full-text assessment to evaluate study eligibility.

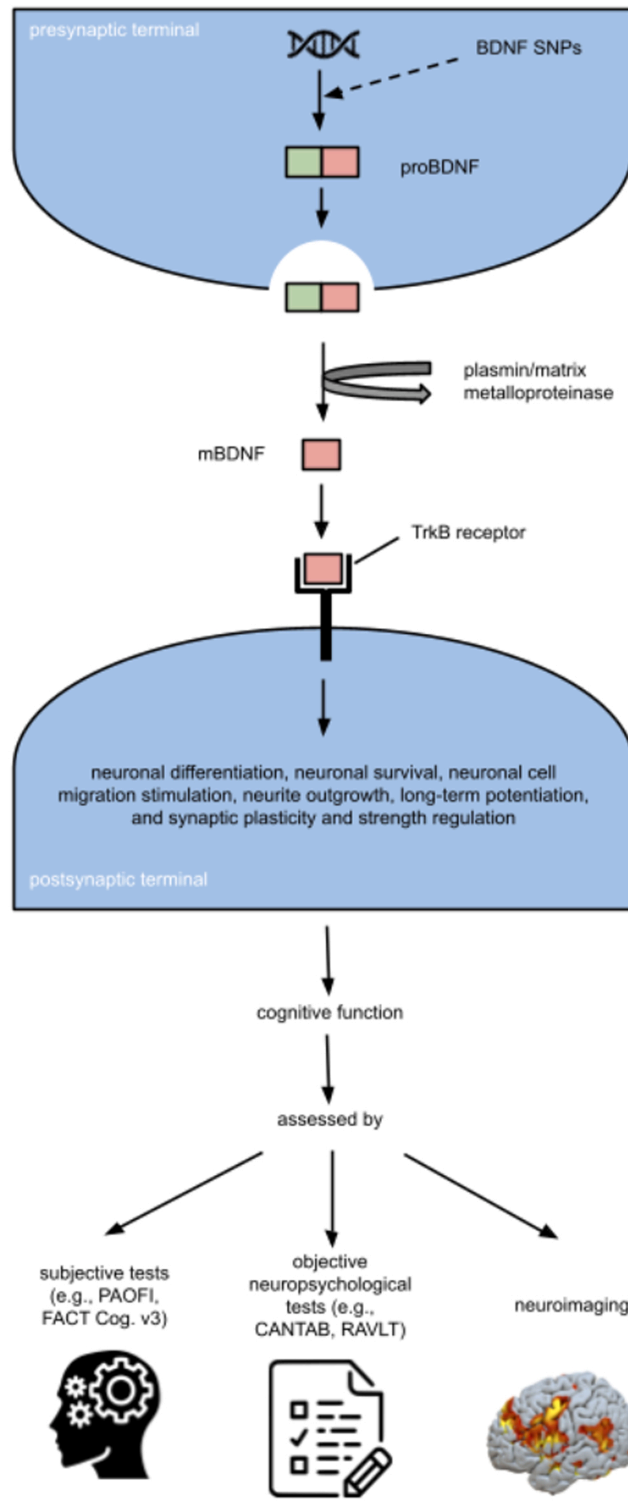

Fig. 1. Schematic illustration of biological processing of BDNF and neurocognition. Abbreviations: BDNF, brain-derived neurotrophic factor; CANTAB, Cambridge Neuropsychological Test Automated Battery; FACT-Cog v3, Functional Assessment of Cancer Therapy-Cognitive Function (version 3); mBDNF, mature brain-derived neurotrophic factor; PAOFI, Psychometric Analysis of the Patient Assessment of Own Functioning Inventory; RAVLT, Rey Auditory Verbal Learning Test; TrkB, tropomyosin receptor kinase B.

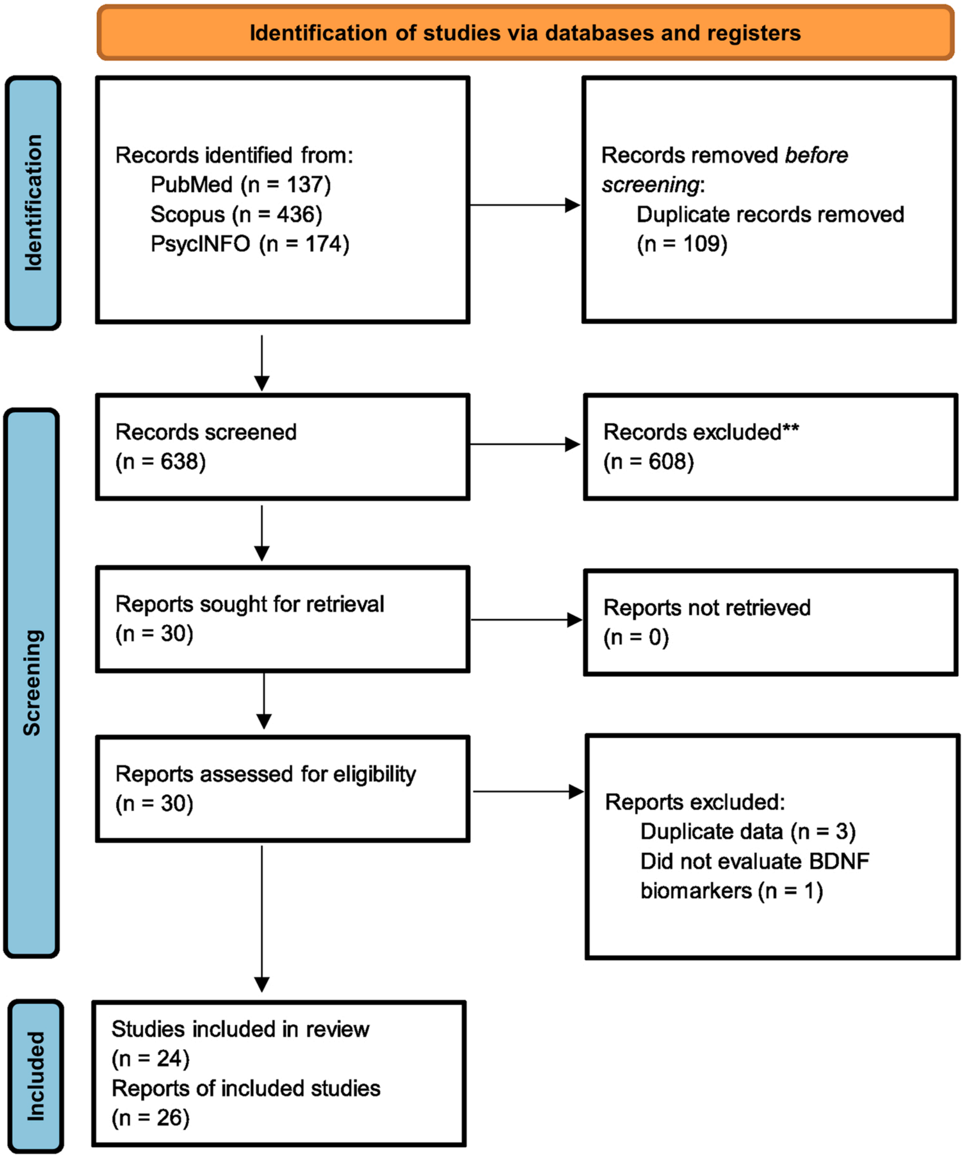

Fig. 2. PRISMA 2020 flow diagram.

2.4. Data extraction and synthesis

Data extraction was completed independently by two authors (DC and PA) and was checked by two authors (DQN and AC). The following data were extracted from the collected studies: study information (study design, subject eligibility criteria, sample size, primary exposures, study participant characteristics, treatments study participants received); BDNF biomarker (protein levels and polymorphisms); neurocognitive outcomes (subjective assessment, objective assessment, or brain function); other significant information (confounding factors and data collection time points). Data synthesis was performed by four authors (DQN, DC, PA, and AC).

2.5. Quality assessment

All authors independently performed quality assessments of the eligible studies. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to evaluate the observational studies' adequacy and comprehensiveness (von Elm et al., 2008). Using the combined STROBE checklist which assessed cohort, case-control, and cross-sectional studies, every observational study was given 1 point for each criterion met, giving a total score out of 22 possible points. For interventional studies, the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines were utilized to assess the transparency and completeness of each clinical trial (Schulz et al., 2010). Using the CONSORT checklist, interventional studies were similarly given 1 point for each criterion met, providing a total score out of 25 possible points.

2.6. Endpoints

In this study, the relationship between BDNF plasma/serum levels and cognitive performances was classified as: (i) positive, (ii) negative, or (iii) null. A positive relationship indicates a statistically significant positive correlation between BDNF levels and cognitive performance, and a negative relationship indicates a statistically significant negative correlation between BDNF levels and cognitive outcomes ($p < 0.05$). A null association indicates a lack of statistically significant association. Among studies designed to evaluate the associations between the *BDNF* gene polymorphisms and cognitive outcomes, the allele or genotype associated with statistically significant better cognitive function was identified. Neuroimaging methods, measures and findings related to

Table 1
Characteristics of eligible studies.

Characteristics	Number of studies, n (%)
Total	26 (100)
Study Design	
Interventional	4 (15)
Observational (cross-sectional)	10 (38)
Observational (longitudinal)	12 (46)
Sample Size	
<100	14 (54)
≥100	12 (46)
Cancer Types	
Breast cancer	13 (50)
Brain cancer	3 (12)
Prostate cancer	2 (8)
Testicular cancer	2 (8)
Hepatocellular carcinoma	2 (8)
Lymphoma	1 (4)
Multiple myeloma	1 (4)
Metastatic cancer	1 (4)
Multiple cancer types[a]	1 (4)
Cognitive Test Type	
Objective	20 (77)
Subjective	12 (46)
Neuroimaging	7 (27)
Objective Cognitive Domains Assessed	
Memory	19 (73)
Executive Function	15 (58)
Attention	15 (58)
Verbal Fluency	11 (42)
BDNF Biomarkers	
Genetic Polymorphism(s)	15 (58)
Serum Levels	8 (31)
Plasma Levels	5 (19)
Intra-tumoral Levels	1 (4)

Abbreviation: BDNF, brain-derived neurotrophic factor.
[a] One study recruited patients with multiple cancer types including osteosarcoma, mixed germ cell tumor, acute lymphoblastic leukemia, colon cancer, Ewing sarcoma, Hodgkin's lymphoma, and hepatocellular carcinoma.

BDNF biomarkers were described.

2.7. Statistical analysis

Descriptive statistics were utilized to report the outcomes. Due to significant heterogeneity in study design, outcome measures, and missing data among the various reviewed studies, meta-analysis was not performed in this review.

3. Results

3.1. Study characteristics

In the first search round, a total of 747 articles were identified, with 109 duplicated, leaving 638 articles to screen (Fig. 2). Of these 638 articles, 26 fulfilled the eligibility criteria, among which close to half were longitudinal observational (46 %) studies, followed by cross-sectional (38 %) studies and interventional (15 %) studies (Table 1). Half (50 %) of the studies included breast cancer patients. The most reported neurocognitive outcomes were objective (77 %), followed by subjective cognitive function (46 %) and neuroimaging (27 %). Fifteen (58 %) studies evaluated the association between *BDNF* polymorphisms and cognitive function, while 14 (54 %) evaluated the association between BDNF levels (plasma, serum or intra-tumoral) with cognitive function.

Among the observational studies (n = 22), key underreported elements included methods to correct for bias (absent in 17 of 22 studies) and sample size calculation (absent in 14 of 22 studies). Among the interventional studies (n = 4), only one study had high methodological quality by reporting of blinding, allocation concealment and sample size calculation methods (Palmer et al., 2020). None of the studies was excluded due to poor methodological quality. Additional information on the quality rating of selected studies is described in supplementary tables 1 and 2.

3.2. BDNF levels and Cognitive Performances in Observational Studies

A total of 10 observational studies assessed the association between BDNF levels and cognitive performances (Table 2) (Altshuler et al., 2019; Bury-Kamińska et al., 2021; Guo et al., 2019; Jehn et al., 2015; Miklja et al., 2022; Schroyen et al., 2021; van Kessel et al., 2022; Yap et al., 2020; Zimmer et al., 2015, 2018). Of these studies, five (50 %) demonstrated a positive association. Four of these studies revealed a positive association between BDNF levels and objective cognitive tests, including patients diagnosed with multiple myeloma (Bury-Kamińska et al., 2021), metastatic cancer (Jehn et al., 2015), B-cell non-Hodgkin lymphoma (B-cell NHL) (Zimmer et al., 2015), and hepatocellular carcinoma (HCC) (Guo et al., 2019). One study evaluated intra-tumoral levels of BDNF in diffuse glioma patients and reported a negative association with memory (van Kessel et al., 2022).

In terms of the association between BDNF levels and self-perceived cognitive function, positive association was observed in one longitudinal observational study involving chemotherapy-receiving early-stage breast cancer (ESBC), with a reduction of BDNF plasma levels observed over the course of chemotherapy, and the reduction trend was associated with the onset of self-perceived cognitive impairment (Yap et al., 2020).

3.3. BDNF levels and Cognitive Performances in Interventional Studies

Four interventional studies utilized a specific intervention (non-pharmacological or pharmacological) in cancer patients or survivors, with BDNF plasma/serum levels and cognition assessed (Table 3) (Gooch et al., 2021; Hartman et al., 2019; Palmer et al., 2020; Tong et al., 2018).

Among the three non-pharmacological studies, the efficacy of computerized-based cognitive activities (Gooch et al., 2021), exercise (Hartman et al., 2019), and acupuncture (Tong et al., 2018) on cognition was evaluated. In a pilot study, adolescent and young adult patients were tasked to complete computerized-based cognitive activities, and cognitive benefits were observed in the processing speed, working memory, and visual attention domains (Gooch et al., 2021). BDNF reduction was observed in both intervention and control arms. However, the correlation between BDNF and cognitive outcomes was not reported. In another randomized controlled trial, breast cancer survivors were randomized to 15 min of moderate-to-vigorous physical activity versus control (Hartman et al., 2019). Improvement of cognitive outcomes was observed in the exercise arm. However, BDNF serum levels were not different between groups, and correlation between BDNF serum levels and cognitive outcomes was not reported. Lastly, in a randomized controlled trial, ESBC patients undergoing chemotherapy received two courses of acupuncture (Tong et al., 2018). BDNF serum levels were increased concerning acupuncture therapy while levels were reduced in the control arm, and a positive association between BDNF serum levels with both subjective and objective cognitive tests was observed.

In terms of pharmacological interventions, there was one randomized controlled trial evaluated the association between BDNF and cognitive function among cancer patients (Palmer et al., 2020). In this study, breast cancer patients receiving melatonin before the first cycle of adjuvant chemotherapy treatment had a more positive cognitive flexibility effect than to the control arm. A reduction of the BDNF levels was observed in the melatonin arm, with an increase of BDNF serum level observed in the placebo arm. However, the change of BDNF serum levels was not associated with cognitive outcomes in the multivariate analysis.

Table 2
BDNF protein levels association with cognition in observational studies (n = 10).

Reference	Population	Objective cognitive test domains	Subjective Cognitive Test	Longitudinal	Source of BDNF	BDNF correlation with cognitive test
Altshuler et al., USA (2019)(Altshuler et al., 2019)	Glioma (n=128)	IM, VCO, L, A, DM, EF	N/A	Yes	plasma	Not reported
Bury-Kaminska et al., Poland (2021)(Bury-Kamińska.et.al., 2021)	Multiple myeloma (n=21)	STAM, STM, LTM, PA, A, EF, VF	N/A	Yes	serum	Positive (STVM, EF)
Guo et al., China (2019)(Guo et.al., 2019)	Hepatocellular carcinoma (HCC) (n=146) HCC complicated with PTSD (n=102) Healthy adults (n=152)	MMSE	N/A	No	serum	Positive (MMSE)
Jehn et al., Germany (2015)(Jehn et al., 2015)	Metastatic cancer (n=59)	VL, M	N/A	No	serum	Positive (STM)
Mikjia et al., USA (2021)(Miklja et al., 2022)	Glioma (n=38)	N/A	Neuro-QOL cognition domain	No	plasma	Not reported
Schroyen et al., Belgium (2021)(Schroyen et al., 2021)	Chemo-treated breast cancer (n=19) Chemo-naive breast cancer (n=18) Healthy adults (n=37)	M, A, PS, EF	N/A	No	plasma	Not reported
van Kessel et al., the Netherlands (2022)(van Kessel et al., 2022)	Diffuse glioma (n=793)	A, EF, M, PS	N/A	No	tumor	Negative (M)
Yap et al., Singapore (2020)(Yap et al., 2020)	ESBC (n=174)	MT, WM, RS, L, M, SA	FACT-Cog v3	Yes	plasma	Positive (FACT-Cog v3)
Zimmer et al., Germany (2014)(Zimmer et al., 2015)	B-cell non-Hodgkin lymphoma (B-cell NHL) (n=30) Healthy adults (n=10)	EF, A	EORTC-QLQ-C30 cognitive function subscale	No	serum	Positive (EF, A)
Zimmer et al., Germany (2018)(Zimmer et al., 2018)	Breast cancer (n=60)	N/A	EORTC QLQ-C30 cognitive function subscale	Yes	serum	null

Abbreviations: A, Attention; DM, Delayed Memory; EF, Executive Function; EORTC QLQ C-30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-Cog v3, Functional Assessment of Cancer Therapy-Cognitive Function (version 3); IM, Immediate Memory; L, Language; LTM, Long-Term Memory; M, Memory; MMSE, Mini-Mental State Exam; N/A, Not Applicable; PA, Planning Ability; PS, Processing Speed; PTSD, Post-Traumatic Stress Disorder; QOL, Quality of Life; RS, Response Speed; SA, Sustained Attention; STAM, Short Term Auditory Memory; STM, Short-Term Memory; STVM, Short-Term Visual Memory; VCO, Visual and Constructional Orientation; VF, Verbal Fluency; VL, Verbal Learning; WF, Word Fluency; WM, Working Memory.

3.4. BDNF Polymorphisms and Cognitive Performances

Fifteen observational studies assessed the relationship between genetic polymorphism of the *BDNF* gene and cognitive function (Table 4) (Altshuler et al., 2019; Barratt et al., 2015; Buskbjerg et al., 2021b; Buskbjerg et al., 2021a; Buskbjerg et al., 2022; Carroll et al., 2019; Cheng et al., 2016; Correa et al., 2016; Dooley et al., 2016; Guo et al., 2019; Harrison et al., 2021; Li et al., 2020; Miklja et al., 2022; R. Buskbjerg et al., 2021; Tan et al., 2019). All studies evaluated the effect of the rs6265 polymorphism on cognition, with the majority of the studies (80 %) failing to show an association. These studies involved different study designs (nine were cross sectional, and six were longitudinal), and patients were diagnosed with various cancer types. One study was a replication and meta-analysis of two cohorts of ESBC patients receiving chemotherapy, with the protective effect of cognitive function observed among Met allele carriers (Tan et al., 2019). Two other studies, both longitudinal studies involving newly diagnosed glioma patients (Altshuler et al., 2019) and HCC patients (Guo et al., 2019), have shown a protective effect on cognition in expressing the homozygous Val alleles.

Two studies (Correa et al., 2016; Guo et al., 2019) evaluated *BDNF* genetic polymorphisms other than rs6265. In one study, four other *BDNF* SNPs (rs10767664, rs10835210, rs110030104, rs2030324) demonstrated significant associations with memory tests (Correa et al., 2016). In another study, *BDNF* SNP G11757C was not associated with cognition function in HCC patients (Guo et al., 2019).

No interventional studies were designed to evaluate the association between BDNF genotypes and cognitive outcomes.

3.5. BDNF and detected changes in neuroimaging studies

Of the seven studies (Buskbjerg et al., 2021b; Buskbjerg et al., 2021a; Buskbjerg et al., 2022; Correa et al., 2016; Harrison et al., 2021; R. Buskbjerg et al., 2021; Schroyen et al., 2021) investigating neuroimaging parameters, six (86 %) analyzed the anatomical effects of cancer and chemotherapy on brain (Buskbjerg et al., 2021b; Buskbjerg et al., 2021a; Buskbjerg et al., 2022; Correa et al., 2016; Harrison et al., 2021; R. Buskbjerg et al., 2021), five (71 %) performed brain connectome analysis (Buskbjerg et al., 2021b; Buskbjerg et al., 2021a; Buskbjerg et al., 2022; Harrison et al., 2021; R. Buskbjerg et al., 2021), one (14 %) completed functional neuroimaging (Harrison et al., 2021), and one (14 %) quantified the degree of neuroinflammation with PET-MRI (simultaneous positron emission tomographic and magnetic resonance imaging) scans using [^{18}F]DPA714 translocator protein (Schroyen et al., 2021) (Table 5). Only three (43 %) of these studies reported associations between neuroimaging and BDNF biomarkers (Correa et al., 2016; Harrison et al., 2021; Schroyen et al., 2021). One study observed that plasma BDNF levels were positively associated with local glial hyperactivation, suggesting BDNF's involvement in neuroinflammation (Schroyen et al., 2021). The remaining two studies examined the association of *BDNF* rs6265 and neuroimaging provided opposite findings. One study observed a lack of significant association between rs6265 (as well as other *BDNF* SNPs) with white matter abnormalities, (Correa et al., 2016) while the other reported lower regional connectivity in left calcarine, left cuneus, and right and left paracentral lobules in chemotherapy-treated breast cancer patients who were *BDNF* Met carriers (Harrison et al., 2021). It is important to note that all three studies adopted a cross-sectional study design, although two studies recruited breast cancer patients (chemotherapy-treated and

Table 3
BDNF serum/plasma levels association with cognition in interventional studies (n = 4).

Reference	Population	Intervention	Objective cognitive test domains	Subjective cognition tests	Intervention efficacy on cognition	Source of BDNF	BDNF correlation with cognition
Gooch et al., USA (2021)(Gooch et al., 2021)	Intervention group (n=6): osteosarcoma (n=2), mixed germ cell tumor (n=1), acute lymphoblastic leukemia (n=1), others (n=2) Control group (n=7): osteosarcoma (n=1), mixed germ cell tumor (n-2), acute lymphoblastic leukemia (n=2), others (n=2)	Intervention: Computer-based cognitive activities for 20-30 minutes daily for 16 weeks following Control: continued with their daily activities such as playing video or computerized games.	PS, VA, VL, WM, EF	N/A	Positive (PS, VA, WM)	serum	Not reported
Hartman et al., USA (2019)(Hartman et al., 2019)	Breast cancer survivors (n=87)	Intervention: participants had a self-set physical activity starting goal, with the encouragement to gradually increase exercise a weekly minimum of 150 minutes of MVPA measured on a Fitbit; A phone call was made during week two and week 6 to patients, where interventionists provided feedback on their Fitbit data; every 3 days they were sent emails regarding theory-based information and reminding them to wear the Fitbit Control: participants received brief emails every 3 days that discussed health topics related to breast cancer that were strictly informational so that behavioral change was not encouraged	PS	PROMIS cognitive abilities	Positive (PS, PROMIS)	plasma	Not reported
Palmer et al., USA/ Brazil (2020)(Palmer et al., 2020)	Intervention group: breast cancer (n=18) Control placebo group: breast cancer (n=18)	Intervention: 20 mg of melatonin for 10 days beginning three days prior to first adjuvant chemotherapy cycle Control: placebo capsules contained only cellulose for 10 days	PS, DA, CF, EM, VL, SI, MR, IR, LK, LRA, ECA, RI	N/A	Positive (CF)	serum	null
Tong et al., China (2018) (Tong et al., 2018)	ESBC n=80	Intervention: Patients received two 4-week courses of acupuncture with a 3-day rest between the 2 courses. Every week, patients were treated once a day for 5 days, followed by 2 days of rest Control: not treated with acupuncture, cognitive behavioral therapy, or yoga	M, DR, STM, R, L, SM, VF, A, PS, VWM, EF, LTM	FACT-Cog v3	Positive (FACT-Cog v3, MR, CDT)	serum	Positive (FACT-Cog v3, MR, CDT)

Abbreviations: A, Attention; CF, cognitive flexibility; DA, Divided Attention; DM, Delayed Memory; DR, Delayed Recall; EF, Executive Function; ECA, Executive Control Abilities; EM, Episodic Memory; ESBC, Early Stage Breast Cancer; FACT-Cog v3, Functional Assessment of Cancer Therapy-Cognitive Function (version 3); IR, Information Retention; L, Language; LK, Lexical Knowledge; LRA, Lexical Retrieval Ability; LTM, Long-Term Memory; M, Memory; MR, Memory Recognition; MVPA, moderate-to-vigorous physical activity; N/A, Not Applicable; PROMIS, Patient-Reported Outcomes Measurement Information System; PS, Processing Speed; R, Recognition; Response Inhibition; SI, Susceptibility to Interference; STM, Short-Term Memory; VA, Visual Attention; VF, Verbal Fluency; VL, Verbal Learning; VWM, Visual Working Memory; WM, Working Memory.

naive) and healthy controls to isolate the effects of cancer from chemotherapy (Harrison et al., 2021; Schroyen et al., 2021). The remaining study involved brain tumor patients who were at least 3 months post-completion of chemotherapy and/or radiation (Correa et al., 2016).

4. Discussion

This review marks the first report that systematically evaluated the associations between BDNF biomarkers and neurocognitive outcomes among cancer patients. Consistent with studies conducted in non-cancer populations (Gunstad et al., 2008; Shimada et al., 2014; Teixeira et al., 2010; Zhang et al., 2012), several reviewed studies (Bury-Kamińska et al., 2021; Jehn et al., 2015; Yap et al., 2020; Zimmer et al., 2015) provided evidence of similar positive associations between BDNF plasma/serum levels and cognitive function among cancer patients and survivors. Neuroimaging studies have reported the link between BDNF biomarkers with neuroinflammation, brain structural changes and connectivity changes. On the contrary, the impact of *BDNF* gene polymorphisms on cognition in cancer patients remains unclear. Collectively, these reports provide key evidence that BDNF is a potential biomarker for monitoring cognitive health in patients and survivors of cancer, although the findings should be validated in large cohorts which are designed to evaluate BDNF-cognition association in cancer.

To establish BDNF as a marker for cognitive health, it is important to assess its predictability for cognitive function and the feasibility of accessing the biomarker. The World Health Organization defines a biomarker as a substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease (Strimbu & Tavel, 2010). In most of the reviewed studies, serum and plasma levels were used as surrogate markers of CNS BDNF, with none utilizing CNS BDNF as a biomarker. BDNF can bidirectionally cross the human blood-brain barrier, (Pan et al., 1998) but despite that brain levels of BDNF are not readily accessible for

Table 4
BDNF Polymorphism rs6265 Association with Cognition in Observational Studies (n = 15).

***BDNF* Polymorphism rs6265 with Cognition in Observational Studies**

Reference	Population	Val/Val (%)	Val/Met (%)	Met/Met (%)	Objective cognitive test domains	Subjective cognitive test	Longitudinal	Allele/Genotype with better cognitive function
Altshuler et al., USA (2019)(Altshuler et al., 2019)	Glioma (n=128)	87 (68)	36 (28)	5 (4)	IM, VPA, L, A, DM, EF	N/A	Yes	Val/Val (VPA, FR)
Baratt et al., Australia/ Norway (2015)(Barratt et al., 2015)	Cancer patients (n=468)	290 (62)	156 (33)	20 (4)	MMSE	N/A	No	null
Buskbjerg et al., Denmark (2021)(Buskbjerg et al., 2021a)	Prostate cancer (n=37)	22 (56)	Not reported		PS, A, WM, VPA, VLM, EF, VL, VF	N/A	Yes	null
	Healthy controls (n=27)	17 (65)	Not reported					
Buskbjerg et al., Denmark (2021)(R. Buskbjerg et al., 2021)	Prostate cancer (n=40)	23 (58)	Not reported		PS, A, WM, VPA, VLM, EF, VL, VF	PAOFI	No	null
	Healthy controls (n=27)	17 (63)	Not reported					
Buskbjerg et al., Denmark (2021)(Buskbjerg et al., 2021b)	Testicular cancer (n=38)	25 (66)	Not reported		PS, A, WM, VPA, VLM, EF, VL, VF	N/A	Yes	null
	Healthy controls (n=21)	14 (68)	Not reported					
Buskbjerg et al., Denmark (2021)(Buskbjerg et al., 2022)	Testicular cancer (n=40)	26 (65)	Not reported		PS, A, WM, VPA, VLM, EF, VL, VF	PAOFI	No	null
	Healthy controls (n=22)	15 (68)	Not reported					
Carroll et al., USA (2019) (Carroll et al., 2019)	Breast cancer (n=319)	179 (56)	102 (32)		A, PS, EF, L, M	FACT-Cog v3	Yes	null
Cheng et al., China (2016)(Cheng et al., 2016)	Triple negative breast cancer (n=80)	22 (28)	42 (52)	16 (20)	MMSE, VF, STM	PRMQ	Yes	null
	Non-triple negative breast cancer (n=165)	47 (29)	80 (48)	38 (23)				
Dooley et al., USA (2016) (Dooley et al., 2016)	Breast cancer (n=112)	75 (67)	37 (33)		N/A	BD-II cognitive dimension of depression	Yes	null
Harrison et al., USA (2021)(Harrison et al., 2021)	Chemo-treated breast cancer (n=42)	Not reported	43%		PS, WM, EF, VF, VM (IM and DR)	N/A	No	null
	Chem-naive breast cancer (n=41)	Not reported	28%					
	Healthy control (n=53)	Not reported	36%					
Li et al., China (2020)(Li et al., 2020)	Breast cancer patients ER-/PR- (n=113)	23 (20)	59 (52)	31 (27)	MMSE, VF, STM, EBPM	N/A	Yes	null
	Breast cancer patients ER+/PR+ (n=119)	30 (25)	57 (48)	32 (27)				
Mikjia et al., USA (2021)(Miklja et al., 2022)	Glioma (n=38)	19 (70)	9 (30)		N/A	Neuro-QOL cognition	No	Not Reported
Tan et al., Singapore (2019)(Tan et al., 2019)	Breast cancer (n=193)	52 (27)	101 (52)	40 (21)	RS, L, M, WM, MT, and SA	FACT-Cog v3	Yes	Met carriers: M, MT, MA)

***BDNF* Polymorphism rs6265 and other SNPs with Cognition in Observational Studies**

Reference	Population	Val/Val (%)	Val/Met (%)	Met/Met (%)	Objective cognitive test domains	Subjective cognitive test	Longitudinal	Allele/Genotype with better cognitive function
Correa et al., USA (2016)(Correa et al., 2016)	Brain tumor (n=150)	Not reported			AA, WM, EF, GS, VF, VM (DR, VL, RM)	N/A	No	• rs6265, rs11030101, rs11030107, rs7127507: null • rs10767664: AT/TT (DR) • rs10835210: AA (DR and RM, vs CC) • rs11030104: AG/GG (DR) rs2030324: AG (EF, vs AA)
Guo et al., China (2019) (Guo et al., 2019)	Hepatocellular carcinoma (HCC) (n=146)	47 (32)	99 (68)		MMSE	N/A	No	rs6265: Val/Val; G11757C: null
	HCC complicated with PTSD (n=102	14 (14)	88 (86)					
	Healthy adults (n=152)	41 (30)	111 (70)					

Abbreviations: A, Attention; AA, Auditory Attention; BD, Beck Depression; BTA – Brief Test of Attention; Chemo, Chemotherapy; CRCI, Cancer-Related Cognitive Impairment; DM, Delayed Memory; DR, Delayed Recall; EF, Executive Function; EBPM, Event-Based Prospective Memory; ER, Estrogen Receptor; FACT-Cog v3, Functional Assessment of Cancer Therapy-Cognitive Function (version 3); FR – Figure Recall; GS, Graphomotor Speed; HVLT-D – Hopkins Verbal Learning Test-Revised Delayed Recall; HVLT-DI – Hopkins Verbal Learning Test-Revised Discrimination Index; IM, Immediate Memory; L, Language; M, Memory; MA, Mental Acuity; MMSE, Mini Mental State Exam; N/A, Not Applicable; PAOFI, Psychometric Analysis of the Patient Assessment of Own Functioning Inventory; PR, Progesterone Receptor; PRMQ, Retrospective Memory and Prospective Memory Questionnaires; PS, Processing Speed; PTSD, Post-Traumatic Stress Disorder; QOL, Quality of Life; R, Recognition; RM, Recognition Memory; RS, Response Speed; SA, Sustained Attention; SNP – Single Nucleotide Polymorphism; STM, Short-Term Memory; TMT-B – Trail Making Test Part B; VPA, Visuospatial Ability; VCO, Visual and Constructional Orientation; VF, Verbal Fluency; VL, Verbal Learning; VLM, Visuospatial Learning and Memory; VM, Verbal Memory; WM, Working Memory.

measurement, requiring the use of a surrogate biomarker such as plasma or serum BDNF level, which are known to correlate with CNS levels (Klein et al., 2011). It is important to note that there are existing literature (Walsh & Tschakovsky, 2018) suggesting that a combination of serum and plasma BDNF, together with the platelet count, will give a more accurate calculation of the BDNF levels.

Additionally, as biomarkers are defined as objective, quantifiable characteristics of biological processes, they do not need to routinely quantify for patients' experience or patients' well-being (Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US), 2016). Consistently observed among the studies we have reviewed, positive association between BDNF plasma/serum levels and cognitive performances are mostly detected using objective cognitive tests. This is an important observation as fluctuation of BDNF levels is associated with psychiatric disorders such as depression (Y. Shi et al., 2020), post-traumatic disorder (Mojtabavi et al., 2020), and schizophrenia (Rodrigues-Amorim et al., 2018), which tend to be subjective in nature.

As a biomarker, BDNF can also contribute to our understanding of the pathological process of CRCI. Aligning with the neuroimaging studies identified in this review, two studies (Dooley et al., 2016; Yap et al., 2021) confirmed that BDNF plays a role in modulating neuroinflammation and brain connectivity. Studies, however, have not determined whether certain patient characteristics, such as cancer types or metastasis status, could mediate the trajectory of cognitive performance associated with BDNF changes. Nonetheless, they could also imply that BDNF blood levels can be broadly applied as a biomarker for monitoring cognitive health across different patient populations.

Besides serum or plasma levels of BDNF, certain *BDNF* SNPs were also being investigated as biomarkers for predicting CRCI. It is hypothesized that polymorphism of the *BDNF* gene can lead to aberrant sorting of pro-BDNF into secretory vesicles, which corresponding decrease activity-dependent secretion of BDNF (Wei et al., 2012). In the literature, the rs6265 polymorphism (also known as Val66Met or G196A) is known to be the most studied *BDNF* SNP (Toh et al., 2018). Based on the studies that we have observed, there is high genetic variability with rs6265, with approximately one-third of the patients being a carrier of the Met allele, making it an excellent genetic variant to study for its predictability with cognitive performances. Disappointingly, most studies did not observe an association between *BDNF* SNPs and cognitive function. It is noteworthy that among the three studies where an association was observed, the direction of the association was not consistent. The finding that a lack of association between *BDNF* SNPs and cognitive function in the majority of the studies is not surprising. We have previously published a systematic review (Toh et al., 2018) of 82 studies evaluating the link between rs6265 and neurocognitive domains which provided us with the same conclusion. This may imply that one single *BDNF* SNP may not be sufficient to establish the link between *BDNF* SNPs and cognitive health. Rather, a polygenic risk score that accounts for multiple SNPs might be required to better understand how *BDNF* SNPs affect BDNF expression and function, leading to cognitive function change.

Besides its remarkable role as a monitoring biomarker, BDNF has great potential to act as a therapeutic target for the management of CRCI. BDNF supplementation is a potential strategy to improve cognitive health in cancer patients/survivors which is currently understudied. Among very limited studies (Gooch et al., 2021; Hartman et al., 2019; Palmer et al., 2020; Tong et al., 2018) designed to improve cognitive performance in cancer patients using a non-pharmacological or pharmacological intervention, we have observed that all reported interventions have successfully improved cognition in the studies. To strengthen the analysis of the relationship between BDNF levels and cognitive function, we highly encourage future interventional studies to investigate the proportional increase of BDNF levels as a surrogate endpoint of CRCI. Studies with an adequately powered sample size will also allow in depth analysis of the correlation between BDNF levels and cognitive function.

Further research is also needed to evaluate the feasibility of augmenting BDNF levels to improve cognitive function. There is a lack of in vivo models to demonstrate whether augmenting BDNF in pre-clinical models improves cognitive function. Pre-clinical models may also allow us to evaluate whether such strategy may translate to a higher risk of toxicities or malignancies, which is unknown with the existing literature. If this approach is tested and found to be successful, identifying an intervention that would consistently increase BDNF to mitigate CRCI would be the following natural step. Finally, the role of BDNF in brain and CNS cancers should be further explored as we observed inconsistent findings with respect to cognition in comparison with other cancer types among the eligible studies. Current reports also suggested a possible role of *BDNF* as an oncogene in brain cancers, although conflicting associations have been observed (Colucci-D'amato et al., 2020).

There are several strengths with this systematic review. First, we have included all studies that have assessed cognitive performance, with at least one form of BDNF biomarkers (levels or polymorphisms) must be measured in the study. This allows us to evaluate studies that have incorporated both BDNF and cognitive outcomes as secondary endpoints, increasing the number of potential studies that are eligible for our study. Furthermore, this review did not limit objective neuropsychology batteries as the only acceptable cognitive performance test. Aligning with the guidance (Wefel et al., 2011) provided by the International Cancer and Cognitive Task Force (ICCTF), we also include studies using self-reported cognitive function (such as FACT-Cog) and neuroimaging as surrogates of cognitive function to allow us to conduct a comprehensive evaluation between BDNF and cognitive performances.

Unfortunately, most of the studies identified in this systematic review contained significant shortcomings, which have limited the interpretability of our study results. First, none of the selected studies were statistically powered to examine the relationship between BDNF and cognitive outcomes as this was not their primary objectives. As a result, many studies had small sample sizes that could generate false-negative or false-positive results. Additionally, most studies utilized many cognitive tests to evaluate cognitive performance; standardization to several suggested domains according to ICCTF would certainly encourage uniformity reporting. Lastly, most of the observational studies were designed as cross-sectional studies, limiting the interpretation of cognitive change over time, potentially threatening the validity of the findings.

5. Conclusions

In conclusion, this systematic review has comprehensively investigated the relationship between BDNF biomarkers and neurocognitive

Table 5
BDNF outcomes association with neuroimaging results (n = 7).

Reference	Population	Study design	Neuroimaging methods	Neuroimaging measures	BDNF biomarkers	Neuroimaging findings
Buskbjerg et al., Denmark (2021)(Buskbjerg et al., 2021a)	Prostate cancer (n=37) Healthy controls (n=27)	Observational (longitudinal)	MRI – DTI and T1-weighted scans	DTI tractography (tract length, number of tracts, FA). Connectome analysis (normalized clustering, normalized path length, SW, global efficiency, local efficiency, normalized node degree, betweenness centrality)	*BDNF* polymorphism	Not reported
Buskbjerg et al., Denmark (2021)(R. Buskbjerg et al., 2021)	Prostate cancer (n=40) Healthy controls (n=27)	Observational (cross-sectional)	MRI – DTI and T1-weighted scans	DTI tractography (tract length, number of tracts, FA). Connectome analysis (normalized clustering, normalized path length, SW, global efficiency, local efficiency, normalized node degree, betweenness centrality)	*BDNF* polymorphism	Not reported
Buskbjerg et al., Denmark (2021)(Buskbjerg et al., 2021b)	Testicular cancer (n=38) Healthy controls (n=21)	Observational (longitudinal)	MRI – DTI and T1-weighted scans	DTI tractography (tract length, number of tracts, FA). Connectome analysis (normalized clustering, normalized path length, SW, global efficiency, local efficiency, normalized node degree, betweenness centrality)	*BDNF* polymorphism	Not reported
Buskbjerg et al., Denmark (2021)(Buskbjerg et al., 2022)	Testicular cancer (n=40) Healthy controls (n=22)	Observational (cross-sectional)	MRI – DTI and T1-weighted scans	DTI tractography (tract length, number of tracts, FA). Connectome analysis (normalized clustering, normalized path length, SW, global efficiency, local efficiency, normalized node degree, betweenness centrality)	*BDNF* polymorphism	Not reported
Correa et al., USA (2016)(Correa et al., 2016)	Brain tumor (n=150)	Observational (cross-sectional)	MRI – FLAIR or T2-weighted sequences	WM abnormalities rating by two neuroradiologists using the modified Fazekas scale	*BDNF* polymorphism	No association between *BDNF* polymorphisms and WM abnormalities.
Harrison et al., USA (2021)(Harrison et al., 2021)	Chemo-treated breast cancer (n=42) Chemo-naive breast cancer (n=41) Healthy control (n=53)	Observational (cross-sectional)	fMRI and rsfMRI – T2-weighted sequences	Global connectome (clustering, path length, SW) Thresholding connectome (AUC) Regional connectome (Network-Based Statistic)	*BDNF* polymorphism	Lower regional connectivity in left calcarine, left cuneus, and right and left paracentral lobules in chemo-treated breast cancer patients who were *BDNF* rs6265 Met carriers.
Schroyen et al., Belgium (2021)(Schroyen et al., 2021)	Chemo-treated breast cancer (n=19) Chemo-naive breast cancer (n=18) Healthy adults (n=37)	Observational (cross-sectional)	[^{18}F]DPA714 simultaneous PET and MRI – 60-min dynamic PET scans, T1-weighted and multi-shell diffusion sequences	Neuroinflammation (VT, VT-ratio) WM structure (fiber density, fiber cross-section, combined measure of fiber density and cross-section)	BDNF plasma levels	Plasma BDNF levels were positively associated with local glial hyperactivation (temporal lobe, putamen, caudate and parietal lobe).

Abbreviations: AUC, Area Under the Curve; Chemo, Chemotherapy; DTI, Diffusion Tensor Imaging; FA, Fractional Anisotropy; FLAIR, Fluid-Attenuated Inversion Recovery; fMRI, Functional MRI; MRI, Magnetic Resonance Imaging. PET, Positron Emission Tomography; rsfMRI, Resting state fMRI; SW, Small-Worldness Index; VT, Total Distribution Volume; WM, White Matter.

function in human studies. We have observed that half of the studies reported positive associations between blood derived BDNF biomarkers (plasma or serum levels) and cognitive function in cancer patients, suggesting that BDNF may serve as a potential monitoring biomarker or even a therapeutic target for mitigating CRCI. Inconclusive findings related *BDNF* SNPs can be explained by the over-emphasis on rs6265 and should be further investigated in combination with other *BDNF* SNPs and polymorphisms of other CRCI-related genes such as *APOE* and *COMT*. Translational studies are required to investigate the most optimal strategies to augment BDNF levels in vivo, to develop appropriate interventions for using the BDNF pathway to improve cognitive health in cancer patients and survivors.

CRediT authorship contribution statement

Conceived and designed the study: **DQN** and **AC**. Acquired and analyzed data: **DQN, DC, PA**, and **AC**. Interpretated data: **DQN, DC, PA, WZ, XX, MA**, and **AC**. Drafted the manuscript: **DQN, DC, PA**, and **AC**. Revised and approved final version of manuscript: **DQN, DC, PA, WZ, XX, MA**, and **AC**.

Conflict of interest

The authors declare no relevant conflicts of interest or financial relationships.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2022.103748.

References

Acheson, A., Conover, J.C., Fandl, J.P., et al., 1995. A BDNF autocrine loop in adult sensory neurons prevents cell death. Nature 374 (6521), 450–453. https://doi.org/10.1038/374450a0.

Altshuler, D.B., Wang, L., Zhao, L., et al., 2019. BDNF, COMT, and DRD2 polymorphisms and ability to return to work in adult patients with low- and high-grade glioma. Neuro Oncol. Pract. 6 (5), 375–385. https://doi.org/10.1093/nop/npy059.

Barratt, D.T., Klepstad, P., Dale, O., Kaasa, S., Somogyi, A.A., 2015. Innate immune signalling genetics of pain, cognitive dysfunction and sickness symptoms in cancer pain patients treated with transdermal fentanyl. PLoS One 10 (9). https://doi.org/10.1371/journal.pone.0137179.

Bury-Kamińska, M., Szudy-Szczyrek, A., Nowaczyńska, A., Jankowska-łęcka, O., Hus, M., Kot, K., 2021. Chemotherapy-related differences in cognitive functioning and their biological predictors in patients with multiple myeloma. Brain Sci. 11 (9) https://doi.org/10.3390/brainsci11091166.

Buskbjerg, C.R., Amidi, A., Agerbaek, M., Gravholt, C.H., Hosseini, S.H., Zachariae, R., 2021b. Cognitive changes and brain connectomes, endocrine status, and risk genotypes in testicular cancer patients–a prospective controlled study. Cancer Med. 10 (18), 6249–6260. https://doi.org/10.1002/cam4.4165.

Buskbjerg, C.R., Amidi, A., Buus, S., Gravholt, C.H., Hadi Hosseini, S.M., Zachariae, R., 2021a. Androgen deprivation therapy and cognitive decline—associations with brain connectomes, endocrine status, and risk genotypes. Prostate Cancer Prostatic Dis. https://doi.org/10.1038/s41391-021-00398-1.

Buskbjerg, C.R., Zachariae, R., Agerbæk, M., et al., 2022. Cognitive impairment and associations with structural brain networks, endocrine status, and risk genotypes in newly orchiectomized testicular cancer patients. Brain Imaging Behav. 16 (1), 199–210. https://doi.org/10.1007/s11682-021-00492-x.

Buskbjerg C, R., Zachariae, R., Buus, S., et al., 2021. Cognitive impairment and associations with structural brain networks, endocrine status, and risk genotypes in patients with newly diagnosed prostate cancer referred to androgen-deprivation therapy. Cancer 127 (9), 1495–1506. https://doi.org/10.1002/cncr.33387.

Carroll, J.E., Small, B.J., Tometich, D.B., 2019. Sleep disturbance and neurocognitive outcomes in older patients with breast cancer: interaction with genotype. Cancer 125 (24), 4516–4524. https://doi.org/10.1002/cncr.32489.

Cheng, H., Li, W., Gan, C., Zhang, B., Jia, Q., Wang, K., 2016. The COMT (rs165599) gene polymorphism contributes to chemotherapy-induced cognitive impairment in breast cancer patients. Am. J. Transl. Res. 8 (11), 5087–5097. Accessed May 30, 2022. /pmc/articles/PMC5126352/.

Cheung, Y.T., Shwe, M., Chui, W.K., et al., 2012. Effects of chemotherapy and psychosocial distress on perceived cognitive disturbances in Asian breast cancer patients. Ann. Pharmacother. 46 (12), 1645–1655. https://doi.org/10.1345/aph.1R408.

Colucci-D′amato, L., Speranza, L., Volpicelli, F., 2020. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. Int. J. Mol. Sci. 21 (20), 1–29. https://doi.org/10.3390/ijms21207777.

Correa, D.D., Satagopan, J., Cheung, K., et al., 2016. COMT, BDNF, and DTNBP1 polymorphisms and cognitive functions in patients with brain tumors. Neuro Oncol. 18 (10), 1425–1433. https://doi.org/10.1093/neuonc/now057.

Dooley, L.N., Ganz, P.A., Cole, S.W., Crespi, C.M., Bower, J.E., 2016. Val66Met BDNF polymorphism as a vulnerability factor for inflammation-associated depressive symptoms in women with breast cancer. J. Affect. Disord. 197, 43–50. https://doi.org/10.1016/j.jad.2016.02.059.

El-Derany, M.O., Noureldein, M.H., 2021. Bone marrow mesenchymal stem cells and their derived exosomes resolve doxorubicin-induced chemobrain: critical role of their miRNA cargo. Stem Cell Res. Ther. 12 (1) https://doi.org/10.1186/s13287-021-02384-9.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2008. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J. Clin. Epidemiol. 61 (4), 344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008.

Food and Drug Administration (US, Bethesda (MD): National Institutes of Health (US), Silver Spring (MD), FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and Other Tools) Resource.BEST (Biomarkers, EndpointS, and Other Tools) Resource. Food and Drug Administration (US), 2016. ⟨https://www.ncbi.nlm.nih.gov/books/NBK326791⟩. (Accessed 30 May 2022).

Gooch, M., Mehta, A., John, T., 2021. Feasibility of cognitive training to promote recovery in cancer-related cognitive impairment in adolescent and young adult patients. J. Adolesc. Young Adult Oncol. https://doi.org/10.1089/jayao.2021.0055.

Gunstad, J., Benitez, A., Smith, J., 2008. Serum brain-derived neurotrophic factor is associated with cognitive function in healthy older adults. J. Geriatr. Psychiatry Neurol. 21 (3), 166–170. https://doi.org/10.1177/0891988708316860.

Guo, J.C., Yang, Y.J., Zheng, J.F., 2019. Functional rs6265 polymorphism in the brain-derived neurotrophic factor gene confers protection against neurocognitive dysfunction in posttraumatic stress disorder among Chinese patients with hepatocellular carcinoma. J. Cell. Biochem. 120 (6), 10434–10443. https://doi.org/10.1002/jcb.28328.

Harrison, R.A., Rao, V., Kesler, S.R., 2021. The association of genetic polymorphisms with neuroconnectivity in breast cancer patients. Sci. Rep. 11 (1) https://doi.org/10.1038/s41598-021-85768-4.

Hartman, S.J., Weiner, L.S., Nelson, S.H., 2019. Mediators of a physical activity intervention on cognition in breast cancer survivors: evidence from a randomized controlled trial. JMIR Cancer 5 (2). https://doi.org/10.2196/13150.

Huang, E.J., Reichardt, L.F., 2001. Neurotrophins: roles in neuronal development and function. Annu. Rev. Neurosci. 24, 677–736. https://doi.org/10.1146/annurev.neuro.24.1.677.

Janelsins, M.C., Heckler, C.E., Peppone, L.J., 2018. Longitudinal trajectory and characterization of cancer-related cognitive impairment in a nationwide cohort study. J. Clin. Oncol. 36 (32), 3231–3239. https://doi.org/10.1200/JCO.2018.78.6624.

Jehn, C.F., Becker, B., Flath, B., 2015. Neurocognitive function, brain-derived neurotrophic factor (BDNF) and IL-6 levels in cancer patients with depression. J. Neuroimmunol. 287, 88–92. https://doi.org/10.1016/j.jneuroim.2015.08.012.

Klein, A.B., Williamson, R., Santini, M.A., 2011. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int. J. Neuropsychopharmacol. 14 (3), 347–353. https://doi.org/10.1017/S1461145710000738.

Kobayashi, L.C., Cohen, H.J., Zhai, W., 2020. Cognitive function prior to systemic therapy and subsequent well-being in older breast cancer survivors: Longitudinal findings from the Thinking and Living with Cancer Study. Psycho Oncol. 29 (6), 1051–1059. https://doi.org/10.1002/pon.5376.

Li, W., Zhao, J., Ding, K., et al., 2020. Catechol-O-methyltransferase gene polymorphisms and the risk of chemotherapy-induced prospective memory impairment in breast cancer patients with varying tumor hormonal receptor expression. Med. Sci. Monit. 26. https://doi.org/10.12659/MSM.923567.

Mayo, S.J., Lustberg, M., M. Dhillon, H., 2020. Cancer-related cognitive impairment in patients with non-central nervous system malignancies: an overview for oncology providers from the MASCC Neurological Complications Study Group. Support. Care Cancer. https://doi.org/10.1007/s00520-020-05860-9.

Miklja, Z., Gabel, N., Altshuler, D., Wang, L., Hervey-Jumper, S.L., Smith, S., 2022. Exercise improves health-related quality of life sleep and fatigue domains in adult high- and low-grade glioma patients. Support. Care Cancer 30 (2), 1493–1500. https://doi.org/10.1007/s00520-021-06566-2.

Mojtabavi, H., Saghazadeh, A., van den Heuvel, L., Bucker, J., Rezaei, N., 2020. Peripheral blood levels of brain-derived neurotrophic factor in patients with posttraumatic stress disorder (PTSD): a systematic review and meta-analysis. PLoS One 15. https://doi.org/10.1371/journal.pone.0241928.

Morris, R.G.M., Anderson, E., Lynch, G.S., Baudry, M., 1986. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319 (6056), 774–776. https://doi.org/10.1038/319774a0.

Ng, T., Dorajoo, S.R., Cheung, Y.T., 2018. Distinct and heterogeneous trajectories of self-perceived cognitive impairment among Asian breast cancer survivors. Psycho Oncol. 27 (4), 1185–1192. https://doi.org/10.1002/pon.4635.

Onishchenko, N., Karpova, N., Sabri, F., Castrén, E., Ceccatelli, S., 2008. Long-lasting depression-like behavior and epigenetic changes of BDNF gene expression induced by perinatal exposure to methylmercury. J. Neurochem. 106 (3), 1378–1387. https://doi.org/10.1111/j.1471-4159.2008.05484.x.

Palmer, A.C.S., Zortea, M., Souza, A., 2020. Clinical impact of melatonin on breast cancer patients undergoing chemotherapy; effects on cognition, sleep and depressive symptoms: a randomized, double-blind, placebo-controlled trial. PLoS One 15 (4). https://doi.org/10.1371/journal.pone.0231379.

Pan, W., Banks, W.A., Fasold, M.B., Bluth, J., Kastin, A.J., 1998. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37 (12), 1553–1561. https://doi.org/10.1016/S0028-3908(98)00141-5.

Rodrigues-Amorim, D., Rivera-Baltanás, T., Bessa, J., et al., 2018. The neurobiological hypothesis of neurotrophins in the pathophysiology of schizophrenia: a meta-analysis. J. Psychiatr. Res. 106, 43–53. https://doi.org/10.1016/j.jpsychires.2018.09.007.

Schroyen, G., Blommaert, J., van Weehaeghe, D., et al., 2021. Neuroinflammation and its association with cognition, neuronal markers and peripheral inflammation after chemotherapy for breast cancer. Cancers 13 (16). https://doi.org/10.3390/cancers13164198.

Schulz, K.F., Altman, D.G., Moher, D., 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann. Intern Med 152 (11), 726–732. https://doi.org/10.7326/0003-4819-152-11-201006010-00232.

Shaker, F.H., El-Derany, M.O., Wahdan, S.A., El-Demerdash, E., El-Mesallamy, H.O., 2021. Berberine ameliorates doxorubicin-induced cognitive impairment (chemobrain) in rats. Life Sci. 269. https://doi.org/10.1016/j.lfs.2021.119078.

Shi, D.D., Dong, C.M., Ho, L.C., Lam, C.T.W., Zhou, X.D., Wu, E.X., Zhou, Z.J., Wang, X. M., Zhang, Z.J., 2018. Resveratrol, a natural polyphenol, prevents chemotherapy-induced cognitive impairment: Involvement of cytokine modulation and neuroprotection. Neurobiol. Dis. 114, 164–173. https://doi.org/10.1016/j.nbd.2018.03.006.

Shi, Y., Luan, D., Song, R., Zhang, Z., 2020. Value of peripheral neurotrophin levels for the diagnosis of depression and response to treatment: a systematic review and meta-analysis. Eur. Neuropsychopharmacol. 41, 40–51. https://doi.org/10.1016/j.euroneuro.2020.09.633.

Shimada, H., Makizako, H., Doi, T., 2014. A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. Front. Aging Neurosci. 6 https://doi.org/10.3389/fnagi.2014.00069.

Strimbu, K., Tavel, J.A., 2010. What are biomarkers? Curr. Opin. HIV AIDS 5 (6), 463–466. https://doi.org/10.1097/COH.0b013e32833ed177.

Tan, C.J., Lim, S.W.T., Toh, Y.L., 2019. Replication and meta-analysis of the association between BDNF Val66Met polymorphism and cognitive impairment in patients receiving chemotherapy. Mol. Neurobiol. 56 (7), 4741–4750. https://doi.org/10.1007/s12035-018-1410-4.

Teixeira, A.L., Barbosa, I.G., Diniz, B.S., Kummer, A., 2010. Circulating levels of brain-derived neurotrophic factor: correlation with mood, cognition and motor function. Biomark. Med. 4 (6), 871–887. https://doi.org/10.2217/bmm.10.111.

Toh, Y.L., Ng, T., Tan, M., Tan, A., Chan, A., 2018. Impact of brain-derived neurotrophic factor genetic polymorphism on cognition: a systematic review. Brain Behav. 8 (7) https://doi.org/10.1002/brb3.1009.

Tong, T., Pei, C., Chen, J., Lv, Q., Zhang, F., Cheng, Z., 2018. Efficacy of acupuncture therapy for chemotherapy-related cognitive impairment in breast cancer patients. Med. Sci. Monit. 24, 2919–2927. https://doi.org/10.12659/MSM.909712.

van Kessel, E., Berendsen, S., Baumfalk, A.E., 2022. Tumor-related molecular determinants of neurocognitive deficits in patients with diffuse glioma. Neuro Oncol. https://doi.org/10.1093/neuonc/noac036.

Walsh, J.J., Tschakovsky, M.E., 2018. Exercise and circulating BDNF: mechanisms of release and implications for the design of exercise interventions. Appl. Physiol., Nutr. Metab. 43 (11), 1095–1104. https://doi.org/10.1139/apnm-2018-0192.

Wefel, J.S., Vardy, J., Ahles, T., Schagen, S.B., 2011. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 12 (7), 703–708. https://doi.org/10.1016/S1470-2045(10)70294-1.

Wei, S.M., Eisenberg, D.P., Kohn, P.D., et al., 2012. Brain-derived neurotrophic factor Val66met polymorphism affects resting regional cerebral blood flow and functional connectivity differentially in women versus men. J. Neurosci. 32 (20), 7074–7081. https://doi.org/10.1523/JNEUROSCI.5375-11.2012.

Yap, N.Y., Tan, N.Y.T., Tan, C.J., 2020. Associations of plasma brain-derived neurotrophic factor (BDNF) and Val66Met polymorphism (rs6265) with long-term cancer-related cognitive impairment in survivors of breast cancer. Breast Cancer Res. Treat. 183 (3), 683–696. https://doi.org/10.1007/s10549-020-05807-y.

Yap, N.Y., Toh, Y.L., Tan, C.J., Acharya, M.M., Chan, A., 2021. Relationship between cytokines and brain-derived neurotrophic factor (BDNF) in trajectories of cancer-related cognitive impairment. Cytokine 144. https://doi.org/10.1016/j.cyto.2021.155556.

Zhang, X.Y., Chen, D.C., Xiu, M.H., et al., 2012. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. Hum. Genet. 131 (7), 1187–1195. https://doi.org/10.1007/s00439-012-1150-x.

Zimmer, P., Baumann, F.T., Oberste, M., et al., 2018. Influence of personalized exercise recommendations during rehabilitation on the sustainability of objectively measured physical activity levels, fatigue, and fatigue-related biomarkers in patients with breast cancer. Integr. Cancer Ther. 17 (2), 306–311. https://doi.org/10.1177/1534735417713301.

Zimmer, P., Mierau, A., Bloch, W., et al., 2015. Post-chemotherapy cognitive impairment in patients with B-cell non-Hodgkin lymphoma: a first comprehensive approach to determine cognitive impairments after treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone or rituximab and bendamustine. Leuk. Lymphoma 56 (2), 347–352. https://doi.org/10.3109/10428194.2014.915546.

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Daniella Chan: Ms. Chan is a Pharmaceutical Sciences undergraduate student researcher attached to Dr Alexandre Chan's laboratory at UCI. Together with Ms. Agrawal, they have led this systematic review as part of the UCI Undergraduate Research Opportunities Program.

Parisa Agrawal: Ms. Agrawal is a Pharmaceutical Sciences undergraduate student researcher attached to Dr Alexandre Chan's laboratory at UCI. Together with Ms. Chan, they have led this systematic review as part of the UCI Undergraduate Research Opportunities Program.

Weian Zhao: Dr Zhao's research interests are to understand and ultimately control the fate of the transplanted stem cells in the body (i.e., where they go and what they do), which will lead to effective and safe clinical medicine. He studies the biological, therapeutic, and detrimental functions of transplanted stem cells in vivo, which will eventually allow us to better utilize them to treat a variety of diseases including cancer and stroke. Furthermore, his research team is developing bioengineered tools including microfluidics, nanoparticles, and aptamers to tackle unmet challenges in disease diagnosis and global health.

Xiangmin Xu: Dr. Xu's research interests are in neural circuitry, which applies to understanding the neurobiology of sensory perception, learning and memory, stress, and epilepsy. Understanding how neural circuits give rise to perception, cognition, and behavior is central to understanding how the brain works and the mechanistic basis of neurological disorders. His research focuses on understanding cell-type specific cortical circuit organization and function, using combined approaches of electrophysiology, optical stimulation and imaging, molecular genetics, and viral tracing.

Munjal Acharya: Dr Acharya's research interests are in neurobiological mechanisms and regenerative medicine approaches to treat cancer and cancer therapy-related cognitive impairments (CRCI). With a blend of molecular, cellular, genetic, and behavioral technique, his team focuses on: (1) glial complement cascade signaling mechanism in cranial radiation therapy and glioblastoma-induced neuroinflammation and cognitive dysfunction, (2) astrocyte-dependent mechanism of radiation-induced cognitive impairments and disruption of circadian rhythm, and (3) human neural stem cell-based regenerative approaches to treat radiation- and chemotherapy-induced cognitive decline and synaptic damage.

Alexandre Chan: Dr Chan's research interests are in cancer supportive care and survivorship clinical studies. The overarching themes of Dr. Chan's research program are to (i) evaluate the mechanisms and biomarkers underlying cancer-related toxicities, (ii) understand the impact of these toxicities on patients' quality of life, (iii) develop pharmacological and non-pharmacological interventions, as well as health services to effectively manage these side effects.