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REVIEW

Genetic Modulation of Neurocognitive Development in Cancer Patients throughout the Lifespan: a Systematic Review

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Abstract

The rise in cancer survival rates has raised concerns about the long-term adverse effects of cancer treatment, including neurocognitive impairment. Neurocognitive deficits such as attention and processing speed are frequently observed and can have a profound, lifelong impact in daily life of cancer patients. Interestingly, large interpatient variability exists in cognitive outcomes. Emerging evidence indicates that such differences may be related to genetic variation. The aim of our review was to systematically summarize the current literature on the modulatory effects of germline genetic polymorphisms on cancer treatment-induced cognitive changes and the potential age-dependent impact in cancer survivors. The PubMed/Medline database was screened using an extensive search string focusing on four components: "cancer", "cancer treatment", "neurocognitive outcome" and "germline genetic variation". Seventeen studies meeting predefined eligibility criteria were analyzed, including sixteen candidate gene studies and one genome-wide association study. 38 polymorphisms in 15 genes across proposed pathophysiological pathways, including (1) neural plasticity and repair, (2) neuroinflammation and defenses against oxidative stress, (3) neurotransmission, and (4) folate metabolism pathway, were reported to be significantly associated with treatment-related neurocognitive dysfunction or neuroimaging abnormalities. Still, some study results remained discordant, partly due to the methodological heterogeneity (i.e. in test assessments, age, cancer-type populations). Future large-scale, (epi-)genome studies integrating neurocognitive assessments and advanced neuroimaging techniques, are recommended in order to investigate neurotoxicity throughout the lifespan. Hence, adverse neurodevelopmental problems during childhood and neurodegenerative processes later in life could be minimized based on genetic risk classifications.

Keywords Genetic predisposition · Neurotoxicity · Cognition · Childhood cancer

Introduction

Major treatment advances have significantly improved the outlook for cancer patients (American Cancer Society, 2015). This improved outlook has raised concerns about long-term adverse effects and the impact on quality of life. One of these adverse effects can be neurological damage. Therapeutic modalities and agents most consistently associated with cognitive impairment in cancer patients include cranial irradiation, intensive systemic and intrathecal chemotherapy, and corticosteroids (Askins, Moore III, & Moore, 2008; Castellino, Ullrich, Whelen, & Lange, 2014; Cole, 2015; Waber et al., 2000; Wolkowitz, Lupien, Bigler, Levin, & Canick, 2004). Human imaging, animal and in vitro studies have supported a neurobiological basis for such cognitive changes (Seigers & Fardell, 2011; Wefel, Vardy, Ahles, & Schagen, 2011). However, many questions still remain regarding treatment effects on the developing brain (i.e. neurodevelopment and neurodegeneration) throughout life. With regard to childhood cancer, up to 40% of survivors may experience neurocognitive deficits (Moore 3rd., 2005).

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Older cancer patients by contrast, might specifically be at risk for early onset dementia (Lange et al., 2014). In this regard, an intriguing observation remains the large degree of interpatient variability in cognitive outcomes. This variability has been related to demographic (e.g., female sex and young age) and treatment variables (e.g., cranial irradiation therapy, intrathecal or high-dose intravenous methotrexate: Buizer, de Sonneville, & Veerman, 2009; Duffner et al., 2014; Hodgson, Hutchinson, Wilson, & Nettelbeck, 2013; Jain, Brouwers, Okcu, Cirino, & Krull, 2009; Krull et al., 2013a, b; Monje et al., 2013; Mrakotsky et al., 2011; Mulhern et al., 2001). Nevertheless, these factors account for only a proportion of the observed variability. Therefore, a compelling need exists to identify additional subject-specific (e.g. environmental or genetic) factors that could more precisely predict which patients could be most at risk for neurocognitive impairment. Childhood cancer patients could particularly be at risk for delayed neurodevelopment, while older cancer patients could be more vulnerable for neurodegenerative processes.

Emerging evidence indicates that several 'germline genetic variants' (i.e. mutations passed on to the offspring by the parent or early in the fertilization process, which is later present in every cell) are linked with cognitive functioning, and may modulate the risk of developing treatment-related neurocognitive deficits (Brouwers, 2005; Cole, 2015). For example, Krull et al. (2013a, b) reported associations between measures of attention and apolipoprotein E (ApoE), methionine synthase (MS), monoamine oxidase A (MAO-A), and glutathione S-transferases (GST) in acute lymphoblastic leukemia (ALL) survivors (Krull et al., 2013a, b).

Given that postnatal brain development during childhood is highly dynamic, children could be particularly vulnerable for neurodevelopmental delay (Stiles & Jernigan, 2010). By contrast, neurodegenerative processes could be accelerated in adult and elderly cancer patients. Cognitive deficits in childhood and adult cancer patients (Askins et al., 2008; Castellino et al., 2014; Krull et al., 2013a, b) can affect long-term academic performance, as well as job success, social functioning and mental health over time, respectively.

Recent neuroimaging studies reported high heritability of neurodevelopmental patterns (Fjell et al., 2015; Thompson et al., 2001). Hence, investigations of specific polymorphisms associated with brain development and interactions with treatments may become more important in the future. Consequently, the genetic research field may offer opportunities to personalize cancer treatment through risk identification, enabling risk-adapted or genotype-tailored treatment regimens or prophylactic interventions. Moreover, this research also holds promise for furthering our understanding of the etiology of treatment-related neurocognitive dysfunction, identifying potential targets for the development of interventions.

As pathophysiological mechanisms are still not fully elucidated, the purpose of this systematic review was to synthetize all current evidence on the modulatory effects of germline genetic polymorphisms on cancer treatment-induced cognitive changes. Moreover, we discuss the current methodological limitations, and may as such present a more distinct lead for future research. A special focus will be given to the importance of expanding this research domain with longitudinal studies, since the high level of neural plasticity, and polymorphisms related to neurodevelopment and neurodegeneration throughout the lifespan will need more attention. Eventually, this knowledge could enable individually tailored therapy to attain the ultimate goal of cancer treatment today, namely, to adapt cures that preserve survivors' long-term neurocognitive abilities and quality of life.

Methods

Search Strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009). A comprehensive literature search was performed using the PubMed/Medline database. The search strategy was based on four mandatory components: "cancer", "cancer treatment", "neurocognitive outcome" and "germline genetic variation". Detailed search terms are presented in Table 1. The search was not narrowed to either pediatric or adult studies, since both neurodevelopmental and degenerative pathways could be affected, albeit with different long-term outcomes (Wefel, Noll, & Scheurer, 2016). We restricted our search to the treatment modalities of radiotherapy, chemotherapeutic agents and corticosteroids, published from 2000 onwards. Given the potential long-term impact on cognitive outcomes, we also searched for studies investigating the occurrence of leukoencephalopathy as the outcome of interest (Cheung et al., 2018).

Study Selection

Publications were deemed eligible for inclusion if they met the following criteria: (1) original research studies in (2) treated (3) human cancer populations, (4) which investigated the modulating effects of germline genetic variation on (5) objective or subjective neurocognitive function, or on the occurrence of leukoencephalopathy. To focus on the long-term effects, (6) all neurocognitive data needed to be collected at least six months after treatment, to exclude (sub)acute, transitory effects. This timing criterion was applied in studies investigating neurocognitive assessments only. With regard to leukoencephalopathy, (7) acute

Table 1 Detailed search terms

Category	Search terms
Cancer	(tumor[Title/Abstract] OR tumors[Title/Abstract] OR tumour[Title/Abstract] OR tumours[Title/Abstract] OR cancer[Title/Abstract] OR cancers[Title/Abstract] OR leukemia[Title/Abstract] OR leukaemia[Title/Abstract] OR medulloblastoma[Title/Abstract] OR glioma[Title/Abstract] OR malignancy[Title/Abstract] OR malignancies[Title/Abstract])
Cancer therapy	(chemotherapy[Title/Abstract] OR chemotherapeutic[Title/Abstract] OR chemoradiotherapy[Title/Abstract] OR chemoradiation[Title/Abstract] OR radiotherapy[Title/Abstract] OR irradiation[Title/Abstract] OR radiation [Title/Abstract] OR radiotherapeutic[Title/Abstract] OR corticosteroids[Title/Abstract])
Neurocognitive outcome	(cognitive[Title/Abstract] OR cognition[Title/Abstract] OR neurocognitive[Title/Abstract] OR neurocognition[Title/Abstract] OR neuropsychological[Title/Abstract] OR neurobehavioral[Title/Abstract] OR neurobehavioural[Title/Abstract] OR neurobehavior[Title/Abstract] OR neurobehaviour[Title/Abstract] OR neurodevelopment[Title/Abstract] OR neurodevelopmental[Title/Abstract] OR neurotoxicity [Title/Abstract] OR chemofog[Title/Abstract] OR chemobrain[Title/Abstract] OR leukoencephalopathy[Title/Abstract] OR memory[Title/Abstract] OR intelligence[Title/Abstract] OR intellect[Title/Abstract] OR intellectual[Title/Abstract] OR attentional[Title/Abstract])
Germline genetic variation	(genetic[Title/Abstract] OR genetics[Title/Abstract] OR gene[Title/Abstract] OR genes[Title/Abstract] OR genotype[Title/Abstract] OR polymorphism[Title/Abstract] OR polymorphisms[Title/Abstract] OR SNP[Title/Abstract] OR SNPs[Title/Abstract] OR pharmacogenomics[Title/Abstract] OR pharmacogenetic[Title/Abstract] OR pharmacogenetics[Title/Abstract] OR genomics[Title/Abstract] OR variant[Title/Abstract] OR variants[Title/Abstract])

investigations were also included, given its possible long-term impact on cognition (Cheung et al., 2018). English publication language was (8) required. Studies were excluded in case of meta-analyses, reviews, commentaries, editorials, conference or workshop abstracts and case studies not related to defined outcomes of interest (e.g., focus on survival or peripheral neuropathy). Preclinical in vitro and animal studies were beyond the scope of this review paper. Studies that used screening instruments only (e.g. MMSE), were also excluded as these are insufficiently sensitive to detect cancer treatment-related neurocognitive dysfunction. Screening of articles was conducted at three sequential levels: (1) titles (2) abstracts (3) full text. Two raters independently rated all titles, abstracts and articles based on the abovementioned criteria. For each stage, an intraclass correlation of .63, .71 and .81, was obtained, respectively. After modification of the 'post-treatment' criterion (i.e. all patients were > 6 months out of treatment, which was not the case or unclear in some of the studies (Amidi et al., 2017; Cheng et al., 2016; Correa et al., 2007; Koleck et al., 2017; Merriman et al., 2014; Ng et al., 2016; Vardy et al., 2015, 2017)), complete consistency was achieved. This systematic screening process was supplemented with a manual search of cited references from retrieved articles. Data were extracted from included publications using a standardized data extraction form. In order to determine risk of biases, information was collected that pertained to geographic location, ethnicity, study design, participant demographics and clinical characteristics, genotyping technique, cognitive assessment tools and timing of assessment. Meta-analysis was not achievable based on the extracted studies, given limited power of single nucleotide polymorphism analyses in small cohorts.

Results

Study and Patient Characteristics

The screening process is summarized in the flow chart presented in Fig. 1. A total of seventeen studies involving 2036 participants with available genotype data were included.

The characteristics of these studies are presented in Table 2. In twelve articles a cross-sectional design was used (Ahles et al., 2003; Bhojwani et al., 2014; Brackett et al., 2012; Cole et al., 2015; Correa et al., 2014a, b, Correa et al., 2016; Howarth et al., 2014; Kamdar et al., 2011; Krull et al., 2008; Krull et al., 2013a, b; Small et al., 2011; Tsujimoto et al., 2016) whereas the remaining five were longitudinal studies (Ahles et al., 2014; Barahmani et al., 2009; Krajinovic et al., 2005; Linnebank et al., 2005, 2009). Only three of these studies explored longitudinal test assessments: in leukemia (Krajinovic et al., 2005), medulloblastoma (Barahmani et al., 2009) and breast cancer (Ahles et al., 2014). The remaining studies investigated MRI scans only ($n = 2$: Linnebank et al., 2005, 2009). Furthermore, only three studies included a healthy control group (Ahles et al., 2014; Brackett et al., 2012; Small et al., 2011).

Sample sizes were usually rather small, with only four studies including more than 200 cancer patients (Bhojwani et al., 2014; Cole et al., 2015; Correa et al., 2014a, b; Krull et al., 2008). Nine studies had clearly defined criteria to exclude patients with a history of events that could negatively impact neurocognitive function (e.g., genetic or neurologic conditions, pre-existing neurocognitive or neuropsychological disorders, head injury: Ahles et al., 2014; Ahles et al., 2003; Correa et al., 2014a, b, Correa et al., 2016; Howarth et al.,

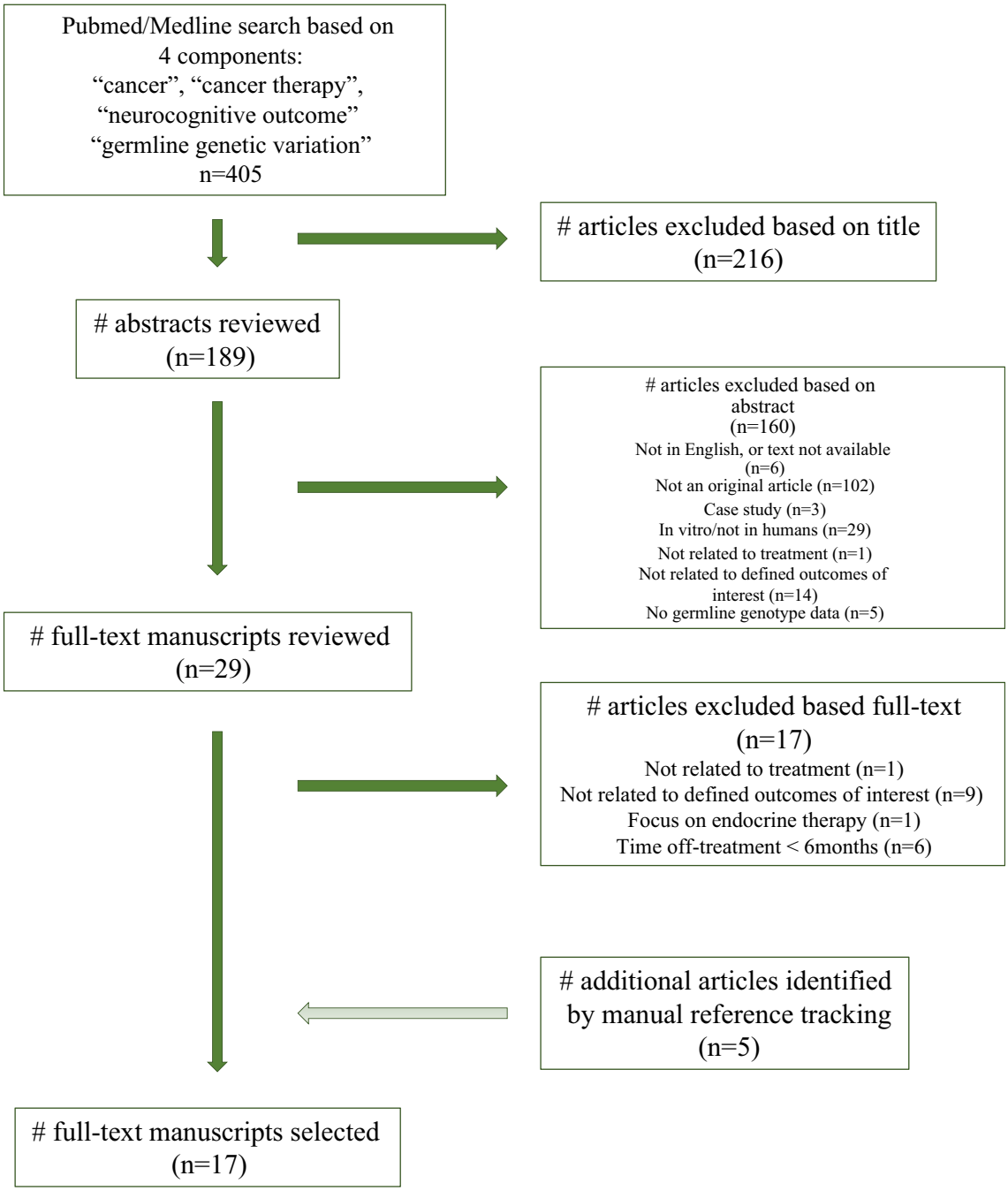


Fig. 1 Flow diagram showing the selection procedure and inclusion-exclusion criteria

2014; Kamdar et al., 2011; Krull et al., 2008; Krull et al., 2013a, b; Small et al., 2011). Studies were conducted in North-America (n = 14), Europe (n = 4), Asia (n = 1). Fourteen studies described the race or ethnicity of their participants, of whom the majority was Caucasian (for details see Table 2: Ahles et al., 2014; Barahmani et al., 2009; Bhojwani et al., 2014; Brackett et al., 2012; Cole et al., 2015; Correa et al., 2016; Howarth et al., 2014; Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2008; Linnebank et al., 2005, 2009; Small et al., 2011).

Equal numbers of studies were conducted in pediatric (n = 10: Barahmani et al., 2009; Bhojwani et al., 2014; Brackett et al., 2012; Cole et al., 2015; Howarth et al., 2014; Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2008; Krull et al., 2013a, b; Tsujimoto et al., 2016) and adult populations (n = 7: Ahles et al., 2014; Ahles et al., 2003; Correa et al., 2014a, b, Correa et al., 2016, Linnebank et al., 2005, 2009; Small et al., 2011).

The most common types of cancer examined were breast cancer (n = 3: Ahles et al., 2014; Ahles et al., 2003), leukemia

Table 2 Description of included studies

Reference (year)	Geographic location; race/ethnicity	Study design; number of study participants with available genotype data	Age (years)		Gender: male/female		Type of cancer examined	Cancer treatment used	Source of DNA sample	Genotyping	Cognitive assessment tools	Time of assessment/ follow-up
			Cases	Controls	Cases	Controls						
Ahles et al. (2003)	USA; NS	Cross-sectional; 80	Mean at assessment: - breast cancer survivors: 55.9 ± 8.8 - lymphoma survivors: 55.8 ± 11.6		16/64		Breast cancer, lymphoma	Systemic standard dose CT regimens	Peripheral blood	PCR – RFLP	i. Verbal ability: Vocabulary (WAIS-III), Reading subtest (WRAT-3), BNT, COWAT ii. Spatial ability: Block Design (WAIS-III) iii. Verbal Learning: CVLT iv. Verbal Memory: Logical Memory I, Stories A & B and Logical Memory Multiple Choice Story B (30′ Delay: WMS-R) v. Visual Memory: Visual Reproduction I and Visual Reproduction II (30′ Delay: WMS-R) vi. Psychomotor function: Digit Symbol (WAIS-III), TMT-A & -B vii. Motor functioning: FTT, Thumb-Finger Sequencing Test viii. Attention (Accuracy): Vigilance and Distractibility subtests (CPT) ix. Attention (Reaction Time): Distractibility and Reaction Time scores (CPT)	Mean = 8.8 ± 4.3 years post--treatment
Linnebank et al. (2005)	Germany; Caucasian	Longitudinal; 42	Mean at diagnosis: 59 ± 11		17/25		PCNSL	"Original Bonn protocol"	NS	PCR - RFLP	Brain MRI (FLAIR and T2-weighted	Before and immediately

Table 2 (continued)

Reference (year)	Geographic location; race/ethnicity	Study design; number of study participants with available genotype data	Age (years)		Gender: male/female		Type of cancer examined	Cancer treatment used	Source of DNA sample	Genotyping	Cognitive assessment tools	Time of assessment/ follow-up
			Cases	Controls	Cases	Controls						
											images): occurrence of leukoencephalopathy	after treatment
Krajinovic et al. (2005)	Canada (n = 14 from non-European descent)	Longitudinal; 90	Med at diagnosis: 5 (1–18)		NS		ALL	DFCI 91–01 and DFCI 95–01 protocols	NS	i. PCR ii. PCR – RFLP iii. ASO hybridization assays	Intelligence scales according to age: - Bayley Scales of Infant Development: <3 years - McCarthy Scales of Children's Abilities: 3–5 years - Wechsler Preschool and Primary Scale of Intelligence-Revised: 5–7 years - WISC-III: 7–16 years - WAIS-R: >16 years	At diagnosis and longitudinally 1–4 years after treatment
Barahmani et al. (2009)	USA; Hispanic ($n = 14$), Non-Hispanic White ($n = 21$), African American ($n = 5$), other (n = 2)	Longitudinal; 42	Range: 3–18		NS		Medulloblastoma	Craniospinal irradiation followed by systemic CT (SJMB96, A9961 regimen B, PBTC-001, POG9031 or POG9233 protocols)	Peripheral blood	Multiplex PCR	Full-scale, verbal, and performance IQ scores measured on the WISC-III	Med follow-up: 3.7 years (2–8.6)
Krull et al. (2008)	USA; Caucasian ($n = 33$) and non-Caucasian ($n = 15$)	Cross-sectional; 48	Mean at diagnosis: 4.1 (0.7–9.1)		32/16		ALL	Various POG protocols (ie, POG 8617, 8698, 8699, 9005, 9006, 9297, 9405, 9406, 9411, 9605)	Peripheral blood	PCR – RFLP	Caregiver behavioral rating using the CSI followed by a brief semistructured clinical interview to clarify diagnostic criteria	Med time off-therapy: 3.8 years (1.5–9.3)
Linnebank et al. (2009)	Germany, Switzerland; Caucasian	Longitudinal; 65	Mean at diagnosis: 59 (28–77)		32/36		PCNSL	"Original Bonn protocol" with intraventricular drug administration	NS	i. PCR – RFLP ii. PCR-based allelic	Brain MRI (FLAIR and T2-weighted images): occurrence of	Before CT and after two cycles of CT

Table 2 (continued)

Reference (year)	Geographic location; race/ethnicity	Study design; number of study participants with available genotype data	Age (years)		Gender: male/female		Type of cancer examined	Cancer treatment used	Source of DNA sample	Genotyping	Cognitive assessment tools	Time of assessment/ follow-up
			Cases	Controls	Cases	Controls						
								and "modified Bonn protocol" without intraventricular therapy		discrimination assays	leukoencephalopathy	
Kamdar et al. (2011)	USA; Hispanic Caucasian ($n = 22$), non-Hispanic Caucasian ($n = 42$), other (n = 8)	Cross-sectional; 72	Mean: - at diagnosis: 4.4 (1.1–10.5) - at follow-up: 3.9 (7.2–18.5)		48/24		ALL	Various POG protocols (ie, POG 8617, 8698, 8699, 9005, 9006, 9297, 9405, 9406, 9411, 9605)	Peripheral blood	i. Taqman genotyping assay ii. PCR	DIVERGT battery: i. Attention and processing speed: TMT-A and -B ii. Fine motor speed: PEGDH and PEGNDH iii. Working memory: DST iv. Executive function: Verbal Fluency Test (CFL)	Time off-treatment (years): - Med: 4.4 - Mean: 5
Small et al. (2011)	USA; primarily White	Cross-sectional; 334: - 130 survivors - 204 HC	Mean: - RT group: 56.93 ± 0.01 - CT group: 51.22 ± 8.63	Mean: 57.07 ± 9.52	All female		Breast cancer	- RT group: only chest wall RT - CT group: chest wall RT + a minimum of 4 cycles of standard-dose CT or a minimum of 4 cycles of standard-dose CT alone	Saliva	Taqman genotyping assay	i. Overall intellectual ability: NART - results expressed as WAIS-R full-scale intelligence scores ii. Episodic memory: 3 items (free recall-short delay, free recall-long delay, and discrimination) from the CVLT and 3 items (immediate recall, delayed recall, and delayed recognition) from the Visual Reproduction subtest of the WMS-III iii. Attention: DST and SST of the WAIS-III and trial 1 from the CTT iv. Complex cognition: Digit Symbol	Mean time off-treatment (months): - RT group: 6.16 ± 1.24 - CT group: 6.64 ± 2.07

Table 2 (continued)

Reference (year)	Geographic location; race/ethnicity	Study design; number of study participants with available genotype data	Age (years)		Gender: male/female		Type of cancer examined	Cancer treatment used	Source of DNA sample	Genotyping	Cognitive assessment tools	Time of assessment/ follow-up
			Cases	Controls	Cases	Controls						
											subtest of the WAIS-III and trial 2 of the CTT v. Verbal fluency: COWAT vi. Motor speed: FTT (dominant and non-dominant hand)	
Brackett et al. (2012)	USA, Canada; primarily White	Cross-sectional; 243: - 109 survivors - 143 healthy siblings	Mean: - at time of study: 30.9 ± 6.06 - at diagnosis: 8.0 ± 0.41	Mean at time of study: 34.3 ± 9.00	56/53	65/78	Medulloblastoma	• CRT mean doses (Gy): - Posterior fossa: 50.4 - Temporal: 43.1 - Frontal: 36.9 - Parietal/occiptal: 40.1 • CT: - Yes: 48.6% - No: 46.8% - Unknown: 4.6%	Buccal cells	i. TaqMan genotyping assay ii. Multiplex PCR	i. CCSS-NCQ ii. BSI-18	Mean time since diagnosis (months): 22.8 ± 4.22
Krull et al. (2013a, b)	USA; White (n = 194), Black (n = 39), others (n = 10)	Cross-sectional; 243	Mean at diagnosis: 6.6 (1.0–18.7)		131/112		ALL	Total XV therapeutic protocol for childhood ALL featuring risk-adapted CT without PCRT	Peripheral blood	i. SNaPshot genotyping assay ii. PCR fragment--size analysis	i. General intelligence: WPPSI-R, WISC-III, or WAIS-III ii. Processing speed: PSI from WISC-III or WAIS-III iii. Working memory: FDI from WISC-III or WAIS-III iv. Sustained attention: beta (response speed), D-prime (attentiveness), and SE of reaction time (variability) indices from the CPT v. Parent-rated attention problems: CPRS	2 years after completion of consolidation therapy
Bhojwani et al. (2014)	USA; NS	Cross-sectional; 364	Med at diagnosis: 5.3 (1.0–18.9)		NS		ALL	Total XV therapeutic protocol for	NS	i. Affymetrix 500 K/6.0 array sets	Brain MRI (FLAIR, T1- and T2-weigthed	At 4 time points during therapy

Table 2 (continued)

Reference (year)	Geographic location; race/ethnicity	Study design; number of study participants with available genotype data	Age (years)		Gender: male/female		Type of cancer examined	Cancer treatment used	Source of DNA sample	Genotyping	Cognitive assessment tools	Time of assessment/ follow-up
			Cases	Controls	Cases	Controls						
								childhood ALL featuring risk-adapted CT without PCRT		ii. Illumina GoldenGate assay	images): occurrence of leukoencephalopathy grade 0 vs >0	
Ahles et al. (2014)	USA; White ($n = 162$), Asian (n = 1), others (n = 3)	Longitudinal; 166: • 55 BC patients treated with CT • 111 controls: - 68 BC patients not treated with CT - 43 HC	Mean: 51.9 ± 7.1	Mean: - BC patient not treated with CT: 56.8 ± 8.3 - HC: 53.0 ± 10.1	All female		Breast cancer	Systemic standard dose CT regimens	Peripheral blood	PCR – RFLP	i. Verbal Ability: Vocabulary (WASI), VFT (D-KEFS) ii. Verbal Memory: CVLT-II, Logical Memory I and II (WMS III) iii. Visual Memory: Faces I and II (WMS III) iv. Working Memory: PASAT v. Processing Speed: Digit Symbol-Coding (WAIS III), TMT (D-KEFS), CWIT (D-KEFS), PEG(N)DH vi. Sorting: Sorting Test (D-KEFS) vii. Distractibility: CPT viii. Reaction Time: CPT ix. Block Design: WASI	- Pretreatment assessment following surgery - Follow-up assessments at 1, 6 and 18 months post-CT
Correa et al. (2014a, b)	USA; NS	Cross-sectional; 211	Mean at study entry: 51 ± 14.2		106/105		Brain tumors	• Conventional fractionated CRT (dose range 2340–6840 cGy) ± CT: $n = 131$ (62%) - Focal RT: $n = 107$ (51%) - Whole-brain RT: $n = 24$ (11%)	Peripheral blood	i. PCR – RFLP ii. PCR – SISAR iii. DNA sequencing iv. GoldenGate genotyping assay	i. Auditory attention: DST of the WMS-III (DS Forward, DS Backward); BTA ii. Executive function: TMT-A & -B; VFT iii. Memory: HVLT-L, −D, -DI Brain MRI (FLAIR and T2-weighted images): rating of	Mean time since treatment completion (months): 44.5 - Completion of RT or CT at least 6 months before enrollment

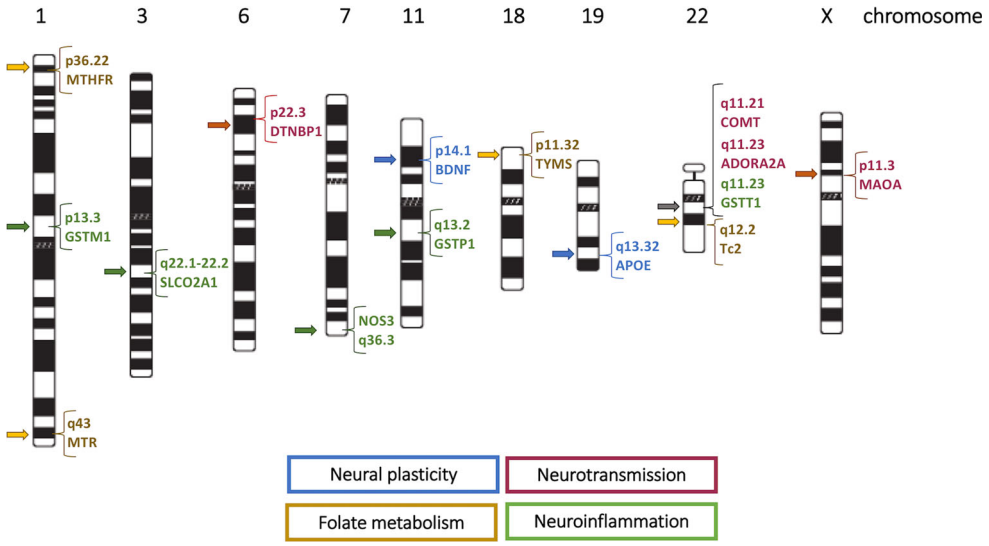
Table 2 (continued)

Reference (year)	Geographic location; race/ethnicity	Study design; number of study participants with available genotype data	Age (years)		Gender: male/female		Type of cancer examined	Cancer treatment used	Source of DNA sample	Genotyping	Cognitive assessment tools	Time of assessment/ follow-up
			Cases	Controls	Cases	Controls						
								• CT-only regimens: $n = 64$ (30%) • No treatment (except for surgical resection): $n = 16$ (8%)			white matter abnormalities	- Surgical resection at least 2 months before accrual if no other treatment was administered
Howarth et al. (2014)	USA; primarily Caucasian	Cross-sectional; 50	Mean: - at time of study: 13.18 ± 2.88 - at time of irradiation: 7.41 ± 3.41		25/25		Brain tumors	- Conformal CRT administered in daily fractions of 1.8 Gy; total radiation dose: 54–59.4 Gy - CT prior to CRT (12%)	Buccal cells	i. PCR- RFLP ii. SNaPshot genotyping	Two experimental, computerized tasks of working memory: SOS-V, -O	Mean time from diagnosis (years): 6.80 ± 2.60
Cole et al. (2015)	USA; White ($n = 308$), Black or African-American ($n = 8$), Asian ($n = 6$), Hispanic ($n = 25$), other ($n = 28$)	Cross-sectional; 350	Med age at time of testing: 10 (6–25)		191/159		ALL	DFCI 91–01 and DFCI 95–01 protocols	Bone marrow	i. Sequenom MassARR-AY iPLEX genotyping platform ii. TaqMan genotyping assays iii. PCR	i. IQ: - 95-01: Vocabulary and Block Design subtests of the WISC-III or WAIS - 00-01: Vocabulary and Matrix Reasoning subtests from the WASI ii. Working memory: age-appropriate Wechsler DST iii. Ability to integrate complex material: Rey-Osterrieth Complex Figure iv. Psychosocial adjustment to everyday life: BASC-2 v. Need for special education services	Med time from diagnosis (years): 5 (3–9)
Correa et al. (2016)	USA; primarily Caucasian	Cross-sectional; 146	Mean at study entry: 51 ± 13.4		68/82		Brain tumors	• CRT (dose range 2340–6840 cGy) ± CT: $n = 105$	Peripheral blood	i. GoldenGate genotyping assay	i. Auditory Attention and Working Memory: DST	Med time off-treatment (months): 27 (6–370)

Table 2 (continued)

Reference (year)	Geographic location; race/ethnicity	Study design; number of study participants with available genotype data	Age (years)		Gender: male/female		Type of cancer examined	Cancer treatment used	Source of DNA sample	Genotyping	Cognitive assessment tools	Time of assessment/ follow-up
			Cases	Controls	Cases	Controls						
								- Focal RT: $n = 85$ - Whole-brain RT: $n = 20$ • CT-only regimens: $n = 45$		ii. Sequenom MassARR-AY iPLEX genotyping platform iii. PCR - RFLP	(DSF, DSB) of the WMS-III; BTA ii. Graphomotor Speed and Executive Functions: TMT-A, -B; VFT iii. Verbal Memory: HVLT-L, −D, -DI Brain MRI (FLAIR and T2-weighted images): rating of white matter abnormalities	
Tsujimoto et al. (2016)	Japan; NS	Cross-sectional; 56	Med at diagnosis: 5 (10 months – 15 years)		29/27		ALL, lymphoma	TCCSG protocol, BFM 95-based regimen protocol, or JPLSG protocol	Peripheral blood/-bone marrow	TaqMan genotyping assay	Brain MRI (FLAIR, T1- and T2-weigthed images): occurrence of leukoencephalopat-hy	Before maintenance therapy or HSCT; patients with clinical symptoms underwent additional imaging after the events

Abbreviations: ALL, acute lymphoblastic leukemia; ASO, allele-specific oligonucleotide hybridization assays; BASC, Behavioral Assessment System for Children; BFM, Berlin-Frankfurt-Munster; BNT, Boston Naming Test; BSI, Brief Symptom Inventory; BTA, Brief Test of Attention; CCSS-NCQ, Childhood Cancer Survivor Study – Neurocognitive Questionnaire; COWAT, Controlled Oral Word Association Test; CPRS, Conners' Parent Rating Scale; CPT, Continuous Performance Test; Med, median; (P)CRT, prophylactic cranial radiotherapy; CSI, Child Symptom Inventory; CT, chemotherapy; CTT, Color Trails Test; CVLT, California Verbal Learning Test; CWIT, Color Word Interference Test; DFCI, Dana Farber Cancer Institute; D-KEFS, Delis-Kaplan Executive Function System; DSB, Digit Span Backward; DSF, Digit Span Forward; DST, Digit Span Test; FDI, Freedom from Distractibility Index; HC, healthy controls; HSCT, hematopoietic stem cell transplantation; HVLT(−L)(−D)(-DI), Hopkins Verbal Learning Test (−Learning: -Delayed Recall: -Discrimination Index); IQ, intelligence quotient; JPLSG, Japan Pediatric Leukemia/Lymphoma Study Group; MMSE, Mini Mental State Examination; MTX, methotrexate; NART, National Adult Reading Test; NS, not specified; PASAT, Paced Auditory Serial Addition Test; PCNSL, primary CNS lymphoma; PEG(N)DH, Grooved Pegboard Test (Non-)Dominant-Hand; PSI, Processing Speed Index; RFLP, restriction fragment length polymorphism; SISAR, Serial Invasive Signal Amplification Reaction; SOS-V/O, Self-Ordered Search-Verbal/Object; SST, Spatial Span Test; TCCSG, Tokyo Children's Cancer Study Group; TMT, Trail Making Test; FTT, Finger-Tapping Test; VFT, Verbal Fluency Test; WAIS(−R), Wechsler Adult Intelligence Scale(-Revised); WASI, Wechsler Abbreviated Scale of Intelligence; WISC, Wechsler Intelligence Scale for Children; WMS(−R), Wechsler Memory Scale(-Revised); WPPSI(−R), Wechsler Preschool and Primary Scale of Intelligence (-Revised); WRAT, Wide Range Achieving Test



Note. SNPs are colored according to their main neurotoxic target. SNPs associated with neural plasticity, neurotransmission, folate metabolism and neuroinflammation are indicated in blue, red, yellow and green, respectively. Location of the gene is indicated on the chromosome (p = short arm, q = long arm). ADORA2A, Adenosine A2A receptor; ApoE, Apolipoprotein E; BDNF, Brain-derived neurotrophic factor; COMT, Catechol-O-methyltransferase; DTNBP1, Dystrobrevin-binding protein1; GST, Gluthation-S-transferase; MAO-A, Monoamine oxidase A; MTHFR, Methylenetetrahydrofolate reductase; MTR, 5-methyltetrahydrofolate-homocysteine S-methyltransferase; MS, Methionine Synthase; NOS3, Endothelial nitric oxide synthase; SLCO2A1, Solute carrier organic transporter 2A1; Tc2, Transcobalamin 2; TSER, Thymidylate synthase enhancer region repeats

Fig. 2 Overview of investigated SNPs, categorized into four main subgroups

(*n* = 7: Bhojwani et al., 2014; Cole et al., 2015; Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2008; Krull et al., 2013a, b; Tsujimoto et al., 2016) and brain tumors (n = 7: Barahmani et al., 2009; Brackett et al., 2012; Correa et al., 2014a, b, Correa et al., 2016; Howarth et al., 2014; Linnebank et al., 2005, 2009). Due to this variety, the investigated treatment regimens were very heterogeneous as well. In all studies, a subgroup of patients had received chemotherapy. Methotrexate (MTX) was part of the chemotherapy regimen in nine studies (Bhojwani et al., 2014; Cole et al., 2015; Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2008; Krull et al., 2013a, b; Linnebank et al., 2005, 2009; Tsujimoto et al., 2016), of which six studies specifically focused on MTX-related neurotoxicity (Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2008; Linnebank et al., 2005, 2009; Tsujimoto et al., 2016). In seven studies, treatment included cranial radiation therapy for at least a subset of patients (Barahmani et al., 2009; Brackett et al., 2012; Cole et al., 2015; Correa et al., 2014a, b; Correa et al., 2016; Howarth et al., 2014; Krajinovic et al., 2005). Thirteen studies analyzed objective or subjective neurocognitive performance as the outcome of interest (Ahles et al., 2014; Ahles et al., 2003; Barahmani et al., 2009; Brackett et al., 2012; Cole et al., 2015; Correa et al., 2014a, b; Correa et al., 2016; Howarth et al., 2014; Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2008; Krull et al., 2013a, b; Small et al., 2011). Objective assessments involved standard international neurocognitive function test batteries, including intelligence testing, as well as computerized tasks assessing processing speed. Subjective assessments included self-report questionnaires and caregiver ratings. In two out of these 13 studies, brain MRI was evaluated as a complement to neurocognitive assessments (Correa et al., 2014a, b; Correa et al., 2016). The remaining four studies evaluated MRI only (Bhojwani et al., 2014; Linnebank et al., 2005, 2009; Tsujimoto et al., 2016). For the studies evaluating neurocognitive performance as the outcome of interest, timing of assessment varied considerably, ranging from an average of 6 months post-treatment to an average of 8.8 years post-treatment.

Thirteen studies used a single bio-specimen type of either blood (*n* = 8: Ahles et al., 2014; Ahles et al., 2003; Barahmani et al., 2009; Correa et al., 2014a, b, Correa et al., 2016; Kamdar et al., 2011; Krull et al., 2008; Krull et al., 2013a, b), buccal cells (*n* = 2: Brackett et al., 2012; Howarth et al., 2014), saliva (Small et al., 2011) or bone marrow (Cole et al., 2015), while one study used blood as well as bone marrow specimens (Tsujimoto et al., 2016). The remaining studies did not report the bio-specimen used for genotyping. Seven studies used a single genotyping assay (Ahles et al., 2014; Ahles et al., 2003; Barahmani et al., 2009; Krull et al., 2008; Linnebank et al., 2005; Small et al., 2011; Tsujimoto et al., 2016), while the remaining studies used multiple genotyping assays. The most commonly used assay techniques were PCR-RFLP (*n* = 9: Ahles et al., 2014; Ahles et al., 2003; Correa et al., 2014a, b, Correa et al., 2016; Howarth et al., 2014; Krajinovic et al.,

Table 3 Genes of interest

Gene	Reference (year)	Population - Pediatric vs adult - Type of cancer examined	Variants investigated	Significant findings	Non-significant findings
1. Neural plasticity and repair					
ApoE	Ahles et al. (2003)	- Adult - Breast cancer, lymphoma	ApoE ε4	↓ visual memory (WMS-R) and block design (Wechsler) in ε4 carriers	tended to score lower in the psychomotor functioning (p50:08) domain as compared to survivors who did not carry an e4 allele. No group differences were found on depression, anxiety, or fatigue. tended to score lower in the psychomotor functioning (p50:08) domain as compared to survivors who did not carry an e4 allele. No group differences were found on depression, anxiety, or fatigue. tended to score lower in the psychomotor functioning (p50:08) domain as compared to survivors who did not carry an e4 allele. No group differences were found on depression, anxiety, or fatigue. Trends in ↓ processing speed (digit symbol and TMT) in ε4 carriers, but non-significant No differences in depression (CES-D), anxiety (STAI), or fatigue (FSI) between ε4 carriers and non-carriers Across all patients, mean scores on cognitive tasks were within the normal range
	Krull et al. (2013a, b)	- Pediatric - ALL		More parent-reported attention problems in ε4 carriers (CPRS) Across all patients, mean scores of attentiveness and response speed (CPT) reached a clinical cut-off (i.e. 1SD)	Across all patients, mean IQ, working memory and processing speed scores (Wechsler), attention subscales (CPT) and parent-reported attention (CPRS) were within the normal range
	Ahles et al. (2014)	- Adult - Breast cancer		Three-way interaction effects between ApoE, smoking and chemotherapy vs. no chemotherapy: - ε4 carriers without smoking Hx treated only with CT: ↓ processing speed (digit symbol, TMT, color-word interference, Pegboard) compared to those with smoking Hx and HC - similar but attenuated findings in patients treated with ET (no chemotherapy) - ε4 carriers without smoking Hx treated treated with ET (no chemotherapy): ↓ processing speed (digit symbol, TMT, color-word interference, Pegboard) and working memory (PASAT) compared to those with smoking Hx and HC	No overall main effects of ApoE (ε4 allele present vs. not present) No two-way interaction ApoE by group effect No two-way interaction effects of APOE4 by smoking. No differences in verbal ability, verbal memory, visual memory, sorting, distractibility, continuous performance test, block design
	Correa et al., (2014a, b)	- Adult - Brain tumors	13 ApoE polymorphisms, including ApoE ε4	- ↓ verbal learning, delayed recall (HVLT) and shifting attention (TMT) in ε4 carriers - ε4 carriers without smoking Hx obtained ↓ attention (BTA) and verbal learning (HVLT) compared to those with smoking Hx - 9 additional ApoE SNPs (rs769446, rs405509, rs429358, rs7412, rs72654473, rs439401, rs5112, rs405697, rs6857) associated with attention, executive functioning or memory	No group differences of ApoE (ε4 allele present vs. not present) were found for brief test of attention (BTA), digit span (Wechsler), verbal fluency A 3-category vascular risk variable (i.e., no vascular risk factors, nonsmoking vascular risk factors, or smoking history) did not moderate the associations between the APOE e4 allele and cognitive test performance Mean cognitive test scores on other measures (not HVLT and TMT) were within the normal range

Table 3 (continued)

Gene	Reference (year)	Population - Pediatric vs adult - Type of cancer examined	Variants investigated	Significant findings	Non-significant findings
				- mean scores of verbal learning (HVLT), and shifting attention (TMT) reached a clinical cut-off (i.e.1 SD) in e4-positive patients	No significant association with leukoencephalopathy
	Correa et al. (2016)	- Adult - Brain tumors		/	No significant interaction effects on cognitive outcomes between the COMT, BDNF, and DTNBP1 SNPs and the APOE ϵ-4 allele No significant association between the cognitive outcomes and APOE ϵ-4 allele No significant association with leukoencephalopathy
	Cole et al. (2015)	- Pediatric - ALL	ApoE ε4	/	No association with cognitive outcomes (IQ, digit span, vocabulary, block design, matrix reasoning, Rey complex figure, parent-reported attention/hyperactivity) Across all patients, obtained mean scores were within the normal range
BDNF	Krull et al. (2013a, b)	- Pediatric - ALL	Val66Met	/	No association with executive outcomes Across all patients, mean IQ, working memory and processing speed scores (Wechsler), attention subscales (CPT) and parent-reported attention (CPRS) were within the normal range
	Correa et al. (2016)	- Adult - Brain tumors	11 BDNF polymorphisms, including Val66Met	- ↓ delayed verbal recall and recognition memory (HVLT) in variant allele carriers of rs10767664 and rs10835210 - ↑ delayed verbal recall memory (HVLT) in variant allele carriers of rs11030104 - ↓ executive functioning (attention shifting TMT, BTA) in variant allele carriers of rs2030324	No association with digit span backwards No significant interactions effects on cognition between BDNF and the APOE ϵ-4 allele, smoking history, vascular risk factors, and treatment with RT ± chemotherapy No significant association with leukoencephalopathy
2. Neuroinflammation and defenses against oxidative stress					
GST	Barahmani et al. (2009)	- Pediatric - Medulloblasto- ma	GSTM1 null GSTT1 null	-↓ full-scale, performance, and verbal IQ in those with at least one null GSTM1 or GSTT1 genotype (homozygous deletion) - patients with GSTM1 or GSTT1 null genotypes obtained clinical scores (i.e. <IQ-1SD), while non-null genotypes obtained scores within the normal range	Age at diagnosis and risk group did not correlate significantly with the genotypes and were not associated significantly with IQ change in time
	Brackett et al. (2012)	- Pediatric - Medulloblasto- ma	GSTM1 null GSTT1 null GSTP1: - 1404A > G (Ile105Val)	Greater anxiety, depression, somatic complaints and psychological distress (BSI) in those with the GSTM1 null genotype (homozygous deletion). Mean self-reported neurocognitive scores remained within the normal range	No significant associations between outcomes and GSTT1, nor GSTP1 No significant differences in self-reported neurocognitive values (CCSS-NCQ) between genotypes
	Krull et al. (2013a, b)	- Pediatric - ALL	- 2294C > T (Ala114Val)	- ↓ attentiveness (CPT) in those carrying the GSTT1 null or GSTP1 polymorphisms (homozygous deletion) - ↑ reaction time variability (CPT) in those with the GSTT1 null genotype (homozygous deletion) - Across all patients, mean scores of attentiveness and response speed (CPT) reached the clinical cut-off (i.e. 1SD)	No significant associations with response speed (CPT) No association between GSTP1 and reaction time variability (CPT) Across all patients, mean IQ, working memory and processing speed scores (Wechsler), attention subscales (CPT) and parent-reported attention (CPRS) within the normal range
	Cole et al. (2015)	- Pediatric	GSTP1:		

Table 3 (continued)

Gene	Reference (year)	Population - Pediatric vs adult - Type of cancer examined	Variants investigated	Significant findings	Non-significant findings
		- ALL	- 1404A > G (Ile105Val) - 2294C > T (Ala114Val)	↓ estimated IQ and digit span scores in those with at least one GSTP1 2294C > T allele (dominant), in a linear prediction	No significant prediction of impairment (dichotomized variable defined as IQ scores <85 and subscale scores <7) No association with vocabulary, block design, matrix reasoning, Rey complex figure, attention, hyperactivity Across all patients, mean scores were within the normal range.
NOS3	Krajinovic et al. (2005)	- Pediatric - ALL	-786 T > C 894G > T	↓ IQ over time in those with NOS3 894 T homozygosity, but only in case of cranial irradiation (recessive) Mean IQ scores remained within the normal range (i.e. 1SD)	No significant association with IQ in non-irradiated patients
	Cole et al. (2015)	- Pediatric - ALL	894G > T	↓ estimated IQ, vocabulary and matrix reasoning in those with NOS3 894 T homozygosity (recessive)	No significant prediction of digit span, block design or parent-reported hyperactivity or attention
SLCO2A	Cole et al. (2015)	- Pediatric - ALL	rs7625035 A > G	↓ estimated IQ, digit span, block design and parent-reported attention scores in those carrying the variant G allele	No significant prediction of vocabulary, matrix reasoning parent-reported hyperactivity Across all patients, mean scores were within the normal range
3. Neurotransmission					
ADORA2A	Tsujimoto et al. (2016)	- Pediatric - ALL, lymphoma	rs576041 rs2298383	- ↑ risk of leukoencephalopathy in those with the rs2298383 CC genotype (recessive) in addition to the MTX concentration as risk factor.	No association with rs2298383 (no additive, no recessive, nor dominant model was significant)
COMT	Small et al. (2011)	- Adult - Breast cancer	Val158Met	- ↓ attention (digit span and spatial span), verbal fluency (COWA) and motor speed (FTT) in Val carriers - Val carriers treated with CT showed ↓ attention (digit span and spatial span) compared to HC Val-carriers	No association with executive functioning, episodic memory, reading or overall intelligence No interaction effect between COMT and RT vs chemotherapy Number of impaired patients was very limited (i.e. up to 11% of RT group, up to 20% in chemotherapy group, defined as 1.5SD below the norm scores) Patients obtained mean scores within the normal range
	Krull et al. (2013a, b)	- Pediatric - ALL		/	No association with executive outcomes Across all patients, mean IQ, working memory and processing speed scores (Wechsler), attention subscales (CPT) and parent-reported attention (CPRS) were within the normal range
	Howarth et al. (2014)	- Pediatric - Brain tumors		↓ verbal working memory (SOS-V) in Met homozygotes compared to Val/Met heterozygotes (dominant)	No difference between Val/Met and Val homozygotes No association with intelligence estimates, nor with visual working memory Across all patients, mean IQ scores were within the normal range
	Cole et al. (2015)	- Pediatric - ALL		↑ parent-reported inattention and hyperactivity (BASC-2) in Met homozygotes (recessive)	No association with intelligence subscales (IQ, digit span, vocabulary, matrix reasoning) Across all patients, mean scores were within the normal range
	Correa et al. (2016)	- Adult - Brain tumors	20 COMT polymorphisms,	- ↓ delayed verbal recall (HVLT) in Val homozygotes relative to Met homozygotes (recessive)	No significant interactions effects on cognition between COMT and the APOE ϵ-4 allele, smoking history,

Table 3 (continued)

Gene	Reference (year)	Population - Pediatric vs adult - Type of cancer examined	Variants investigated	Significant findings	Non-significant findings
			including Val158Met	- 10 additional COMT SNPs (rs4818, rs9332377, rs5746847, rs165815, rs5993883, rs4646312, rs740603, rs165774, rs6269, rs4646316) associated with ↓ digit span, attention (TMT), executive functioning (BTA), verbal fluency or memory (HVLT)	vascular risk factors, and treatment with RT ± chemotherapy No significant association with leukoencephalopathy
DTNB1	Correa et al. (2016)	- Adult - Brain tumors	7 DTNBP1 polymorphisms	↓ verbal recognition memory (HVLT) in variant allele carriers of rs742106	No association with digit span, nor with brief test of attention No significant interactions effects on cognition between DTNB1 and the APOE ε-4 allele, smoking history, vascular risk factors, and treatment with RT ± chemotherapy No significant association with leukoencephalopathy
MAO-A	Krull et al. (2013a, b)	- Pediatric - ALL	941G > T 1460 T > C	↑ reaction time variability (CPT) in those carrying the MAO-A 1460 T > C polymorphism (dominant) Across all patients, mean scores of attentiveness and response speed (CPT) reached the clinical cut-off (i.e. 1SD), whereas reaction time variability (CPT) did not	No association with response speed, nor attentiveness (CPT) No association between 941G > T and any attention values (CPT) Across all patients, mean IQ, working memory and processing speed scores (Wechsler) and parent-reported attention (CPRS) were within the normal range
	Cole et al. (2015)	- Pediatric - ALL	1460 T > C	/	No association with cognitive outcomes (IQ, digit span, vocabulary, block design, matrix reasoning, Rey complex figure, parent-reported attention/hyperactivity) Across all patients, mean scores were within the normal range
4. Folate pathway metabolism					
MTHFR	Linnebank et al. (2005)	- Adult - PCNSL	677C > T	Occurrence of leukoencephalopathy predicted by a combined risk haplotype, defined as presence of homozygosity of MTHFR 677TT or transcobalamin 2776GG (recessive) or MTR 2756 G carriers (AG/GG: dominant)	Each of the three polymorphisms was over-represented among patients with leukoencephalopathy, but after correction for multiple testing, none of the polymorphisms alone referred a significant association with leukoencephalopathy
	Krajinovic et al. (2005)	- Pediatric - ALL	677C > T 1298A > C	/	No significant IQ changes over time in 677C > T carriers
	Krull et al. (2008)	- Pediatric - ALL		-More ADHD inattentive symptoms in 1298A > C carriers (dominant), with a 7.4 increase in risk for ADHD diagnosis -The combined risk haplotype of C677T/A1298C was associated with increased rates of ADHD symptoms −22.9% of the patients obtained a clinical cut-off score (i.e. 21/36) of inattention (CSI)	-A1298C polymorphism was not significantly related to the hyperactivity subtype −1.3-fold increased risk for ADHD diagnosis in 677C > T carriers, but non-significant association
	Linnebank et al. (2009)	- Adult - PCNSL		Occurrence of leukoencephalopathy predicted by 677TT and 1298AA homozygous genotypes (recessive)	/
	Kamdar et al. (2011)	- Pediatric - ALL		↑ global cognitive impairment (DIVERGT battery, defined as one standard score < 70 or 2 standard scores <80) in 1298A > C carriers Such impairment was observed in 44.3% of the study population	No association with basic and motor speed, nor significant differences between 677C > T carriers vs. non-carriers. Across all patients, mean scores were within the normal range

Table 3 (continued)

Gene	Reference (year)	Population - Pediatric vs adult - Type of cancer examined	Variants investigated	Significant findings	Non-significant findings
				↓ executive functioning (shifting attention on TMT) in 1298A > C carriers	
	Krull et al. (2013a, b)	- Pediatric - ALL		/	No association with executive outcomes (processing speed and parent-reported attention) for any of the two genotypes
	Cole et al. (2015)	- Pediatric - ALL		/	No association with cognitive outcomes (IQ, digit span, vocabulary, block design, matrix reasoning, Rey complex figure, parent-reported attention/hyperactivity) for any of the two genotypes for any of the two genotypes Across all patients, mean scores were within the normal range
	Tsujimoto et al. (2016)	- Pediatric - ALL, lymphoma	677C > T	/	No association with leukoencephalopathy (no additive, no recessive, nor dominant model was significant)
MTR	Linnebank et al. (2005)	- Adult - PCNSL	2756A > G	Occurrence of leukoencephalopathy predicted by a combined risk haplotype, defined as presence of homozygosity of MTHFR 677TT or transcobalamin 2776GG (recessive) or MTR 2756 G carriers (AG/GG: dominant)	Each of the three polymorphisms was over-represented among patients with leukoencephalopathy, but after correction for multiple testing, none of the polymorphisms alone referred a significant association with leukoencephalopathy
	Krajinovic et al. (2005)	- Pediatric - ALL		/	No association with IQ changes over time
	Linnebank et al. (2009)	- Adult - PCNSL		/	No association with occurrence of leukoencephalopathy
	Kamdar et al. (2011)	- Pediatric - ALL		↓ global cognitive impairment (DIVERGT battery, defined as one standard score < 70 or 2 standard scores <80) in 2756AA genotype (recessive) Such impairment was observed in 44.3% of the study population ↓ basic focused attention (TMT) in 2756AA genotype (recessive) ↓ fine motor speed non-dominant hand (PEGNDH) in 2756AA genotype (recessive)	No association with shifting attention (TMT) Across all patients, mean scores were within the normal range
	Krull et al. (2013a, b)	- Pediatric - ALL		↓ attentiveness and response speed (CPT) in 2756A > G carriers Across all patients, mean scores of attentiveness and response speed (CPT) reached the clinical cut-off (i.e. 1SD)	No association with reaction time variability (CPT) Across all patients, mean IQ, working memory and processing speed scores (Wechsler), attention subscales (CPT) and parent-reported attention (CPRS) were within the normal range
Tc2	Linnebank et al. (2005)	- Adult - PCNSL	776C > G	Occurrence of leukoencephalopathy predicted by a combined risk haplotype, defined as presence of homozygosity of MTHFR 677TT or transcobalamin 2776GG (recessive) or MTR 2756 G carriers (AG/GG: dominant)	Each of the three polymorphisms was over-represented among patients with leukoencephalopathy, but after correction for multiple testing, none of the polymorphisms alone referred a significant association with leukoencephalopathy
	Linnebank et al. (2009)	- Adult - PCNSL		Occurrence of leukoencephalopathy predicted by the 776GG genotype (recessive)	/
TSER	Linnebank et al. (2009)	- Adult	28-bp repeat	/	No association with occurrence of leukoencephalopathy

Table 3 (continued)

Gene	Reference (year)	Population - Pediatric vs adult - Type of cancer examined	Variants investigated	Significant findings	Non-significant findings
	Kamdar et al. (2011)	- PCNSL - Pediatric - ALL		↓ executive functioning (shifting attention on TMT) in those with the 2R/3R and 3R/3R genotypes (dominant), compared to 2R/2R	No association with motor speed, nor with cognitive screening battery DIVERGT Across all patients, obtained scores were on average within the normal range
	Cole et al. (2015)	- Pediatric ALL		/	No differences in cognitive outcomes (IQ, digit span, vocabulary, block design, matrix reasoning, Rey complex figure, parent-reported attention/hyperactivity) between 3R/3R vs. 2R/3R or 2R/2R Across all patients, obtained scores were on average within the normal range

This table summarizes the findings on the genes reported to be significantly associated with treatment-related neurocognitive dysfunction, or leukoencephalopathy or leukoencephalopathy, by at least one study. These genes of interest are divided into four categories based on their role in hypothesized molecular mechanisms underlying cancer treatment-induced central neurotoxicity, namely (1) neural plasticity and repair, (2) oxidative stress and neuroinflammation, (3) neurotransmission and (4) folate pathway metabolism. If the term 'carriers' was mentioned in the results, group comparisons were performed between patients carrying at least one specific allele present vs. patients not carrying this allele, suggesting the allele to be dominant. The term 'recessive' was added for studies which compared homozygous to heterozygous polymorphisms

Abbreviations: ↓, worse performance on, or lower; /, no significant associations; ADORA2A, Adenosine A2A receptor; ALL, acute lymphoblastic leukaemia; ApoE, Apolipoprotein E; BDNF, Brain-derived neurotrophic factor; COMT, Catechol-O-methyltransferase; CT, chemotherapy; DTNBP1, Dystrobrevin-binding protein1; ET, endocrine therapy; GST, Gluthation-S-transferase; HC; healthy controls; Hx, history; IQ, intelligence quotient; MAO-A, Monoamine oxidase A; Met, methionine; MTHFR, Methylenetetrahydrofolate reductase; MTR, 5-methyltetrahydrofolate-homocysteine S-methyltransferase; MS, Methionine Synthase; NOS3, Endothelial nitric oxide synthase; PCNSL, primary CNS lymphoma; SLCO2A1, Solute carrier organic transporter 2A1; Tc2, Transcobalamin 2; TSER, Thymidylate synthase enhancer region repeats; Val, valine

2005; Krull et al., 2008; Linnebank et al., 2005, 2009), TaqMan genotyping assay ($n = 5$: Brackett et al., 2012; Cole et al., 2015; Kamdar et al., 2011; Small et al., 2011; Tsujimoto et al., 2016) and GoldenGate genotyping assay ($n = 3$: Bhojwani et al., 2014; Correa et al., 2014a, b, Correa et al., 2016). In the only genome-wide association study (GWAS) included in this review, genotyping was performed using Affymetrix 500 K/6.0 array sets (Bhojwani et al., 2014).

Treatment-Related Neurocognitive Dysfunction and Genotype

One GWAS was identified (Bhojwani et al., 2014), while the remaining studies investigated candidate genes of targeted pathways, that is, isolated single nucleotide polymorphisms (SNPs). A total of 112 polymorphisms involving 46 genes were reported by the candidate gene studies. All studies provided specific hypotheses justifying the selection of the gene(s) and variant(s). Thirty-eight polymorphisms in 15 of the investigated genes were reported to be significantly associated with treatment-related neurocognitive dysfunction, or leukoencephalopathy or white matter changes, in at least one study. These genes could be subdivided into four hypothesized mechanism categories, namely (1) neural plasticity and repair, (2) neuroinflammation and defenses against oxidative stress, (3) neurotransmission and (4) folate pathway metabolism (see Fig. 2).

Below, the results of the studies will be described for each category. A summary of significant findings is presented in Table 3. For a detailed description of the proposed mechanisms, we refer the reader to reviews on this specific topic (McAllister et al., 2004; Saykin, Ahles, & McDonald, 2003).

Candidate Gene Studies

Neural Plasticity and Repair

Apolipoprotein E Gene ApoE is a glycoprotein involved in lipid metabolism that plays an important role in neuronal repair and plasticity after injury (Alvim et al., 2010; Mahley & Huang, 2012). The ApoE gene is polymorphic with three major alleles (ApoE ε2, ε3 and ε4), varying in their amino acids.

Five studies examined the risk of treatment-related neurocognitive impairment associated with ApoE polymorphisms (Ahles et al., 2014; Ahles et al., 2003; Cole et al., 2015; Correa et al., 2014a, b; Krull et al., 2013a, b), of which four found significant associations. With regard to pediatric research, Krull et al. (2013a, b) showed increased parent-reported attention problems in childhood leukemia survivors carrying the ε4 allele (Krull et al., 2013a, b). However, either parent-report or objective measures in survivors of leukemia did not demonstrate such main effects of the ε4 allele (Cole et al., 2015). By contrast, in adult cancer research, Ahles et al. (2003) reported that long-term survivors of breast cancer and lymphoma treated with standard dose chemotherapy who carried at least one ε4 allele performed worse on visual memory and block design, and tended to score lower on processing speed, compared with non-ε4-carriers (Ahles et al., 2003). In contrast to such main effects of the ApoE genotype, two more recent adult studies demonstrated that effects were moderated by smoking in adult breast (Ahles et al., 2014) and brain tumor patients (Correa et al., 2014a, b). Ahles et al. (2014) investigated the relationship between post-treatment cognitive changes, ApoE genotype, and smoking in breast cancer patients (Ahles et al., 2014), longitudinally. The deleterious effect of ApoE ε4 on processing speed was more pronounced in patients treated with chemotherapy compared to primarily endocrine treatment. Furthermore, this effect was moderated by smoking history. Patients carrying the ε4 allele who did not smoke showed worse performance on processing speed and working memory compared to those with a smoking history and healthy controls. Comparable results have been reported by Correa et al. (2014a, b) in a large cohort of adult brain cancer survivors Correa et al. (2014a, b). The authors found that patients with at least one ε4 allele performed worse on verbal learning and delayed recall, and slightly worse on processing speed, relative to ε4-negative patients. Again, smoking seemed to attenuate some of the risk associated with the ε4 genotype. Patients with at least one ε4 allele and a history of smoking scored better on attention and verbal learning. Such interaction effects with smoking are hypothetically due to the influence of both factors on cholinergic activity. As cholinergic activity is strongly associated with experienced stress, future physiological measures of stress-related biomarkers could be interesting in both pediatric and adult populations. The authors identified nine additional ApoE SNPs associated with attention, executive functioning, or memory. None of the SNPs provided a good fit for the white matter abnormality ratings on MRI.

Brain-Derived Neurotrophic Factor (BDNF) Gene BDNF is the most widely distributed neurotrophin in the CNS, particularly in the prefrontal cortex and hippocampus. It has been associated with synaptic plasticity, growth and remodeling of dendrites and axons, and long-term potentiation (Savitz, Solms, & Ramesar, 2006; Teixeira, Barbosa, Diniz, & Kummer, 2010).

We identified two studies which assessed associations between BDNF polymorphisms and cancer-treatment related neurocognitive impairment (Correa et al., 2016; Krull et al., 2013a, b).

No associations were encountered between the SNP rs6265 (Val66Met) and cognitive outcomes in leukemia survivors (Krull et al., 2013a, b) in contrast adult brain tumor patients (Correa et al., 2016). Three BDNF SNPs were related to verbal memory performance (learning, delayed recall, recognition), with variant allele carriers of SNPs rs10767664 and rs10835210 having lower scores, and variant allele carriers of SNP rs11030104 having higher scores. In addition, SNP

rs2030324 was associated with executive functions, with variant allele carriers showing worse performance. No associations were encountered between the SNP rs6265 (Val66Met) and any of the cognitive outcomes, nor between BDNF SNPs and the presence of leukoencephalopathy detected on MRI.

Neuroinflammation and Defenses against Oxidative Stress

Gluthation-S-Transferase (GST) Gene Family: GSTP1, GSTM1, GSTT1 Gluthation-S-transferases are enzymes which catalyze detoxification processes (e.g. by binding glutathione to xenobiotic substrates (such as chemical carcinogens, environmental pollutants, and antitumor agents, or by inactivating secondary metabolites during oxidative stress) (Hayes, Flanagan, & Jowsey, 2005). In the Caucasian population, 42–60% and 13–26% of people have a homozygous deletion of GSTM1 and GSTT1, respectively, which is a so-called null genotype, not expressing the enzymes which possibly leads to elevated risk for biological toxification (Garte et al., 2001).

Three of the four studies (Barahmani et al., 2009; Brackett et al., 2012; Cole et al., 2015; Krull et al., 2013a, b) investigating at least one member of the GST gene family reported significant associations. These genes were only investigated in pediatric cancer patients so far.

Barahmani et al. (2009) longitudinally investigated the relationship between GSTM1 and GSTT1 null genotypes and intelligence test scores in a small cohort of pediatric medulloblastoma patients treated with craniospinal radiation and systemic chemotherapy (Barahmani et al., 2009). They found that patients with at least one null GSTM1 or GSTT1 genotype showed significant declines in Full-Scale, Performance, and Verbal IQ compared to those without null genotypes. The mean intelligence test scores (Full Scale IQ scores) in the null genotype subgroup also reached a cut-off <85 (i.e. 1SD below the population average of FSIQ=100). Complementary to this finding, Brackett et al. (2012) reported that childhood medulloblastoma survivors with the GSTM1 null genotype also showed greater self-reported psychological distress, compared to those with the non-null genotypes (Brackett et al., 2012). However, no association with self-reported neurocognitive functioning emerged in this study (GSTM1, nor GSTP1). Krull et al. (2013a, b) used standardized cognitive assessments in pediatric leukemia survivors. Similar to the findings of Barahmani et al. (2009), leukemia patients who carried the GSTT1 null or GSTP1 polymorphisms demonstrated elevated rates of inattentiveness compared to the general population Krull et al. (2013a, b). Similarly, Cole et al. (2015) reported that pediatric leukemia survivors with at least one GSTP1 T allele had lower estimated intelligence and digit span scores than those who were homozygous for the wild-type C allele (Cole et al., 2015). Nevertheless, the association with impairment was not significant after FDR correction. Although Krull et al. (2013a, b) and Cole (2015) found GSTP1 to be associated with attention and intelligence scores, no association with self-reported complaints was found by Brackett et al. (2012).

Endothelial Nitric Oxide Synthase (NOS3) Gene Endothelial nitric oxide (NO) synthase is an enzyme catalyzing the formation of endothelial nitric oxide. The vasodilator NO is a key mediator regulating the vascular tone, and exhibits antioxidant properties. In the NOS3 gene, a G894 T substitution results in decreased enzyme activity with consequently a diminished capacity for protection against oxidative stress (Sofowora et al., 2001). The two studies examining the effect of NOS3 polymorphisms both reported significant associations in pediatric cancer patients (Cole et al., 2015; Krajinovic et al., 2005).

In a longitudinal study, Krajinovic et al. (2005) found that NOS3 894 T homozygosity was associated with a decline in intelligence scores in leukemia patients, but only in case of cranial irradiation (Krajinovic et al., 2005). Furthermore, the authors observed that the interaction between NOS3 894 T homozygosity and cranial irradiation was more pronounced in patients treated with prednisone (according to the Dana Farber Cancer Institute (DFCI) 1995–2001 protocol; compared to dexamethasone (according to the DFCI 1991-2001 protocol) (Barry et al., 2007). This finding suggests that the neurobehavioral toxicity associated with steroids might interact with chemotherapy and radiation treatment. Cole et al. (2015) expanded this study with a larger cohort of childhood leukemia survivors that included a subset of patients from the study of Krajinovic et al.. They confirmed the association between the NOS3 variant and decreased intelligence scores, with the odds of intelligence impairment (defined as IQ ≤ 85) being approximately five times higher for survivors homozygous for the 894 T allele. However, this study did not report any differences between irradiated patients and non-irradiated patients.

Solute Carrier Organic Transporter 2A1 (SLCO2A1) Gene SLCO2A1 is known as a prostaglandin transporter, which is involved in the uptake and clearance of prostaglandins. Prostaglandins are major lipid mediators that can also influence inflammatory responses such as oxygen radicals within the CNS (Ricciotti & FitzGerald, 2011), and as such can alter the balance between chronic inflammation versus protective mechanisms.

Cole et al. (2015) reported that pediatric leukemia survivors carrying the variant G allele of SLCO2A1 rs762035 obtained lower mean estimated intelligence scores and lower working memory scores than those who were homozygous for the wild-type C allele (Cole et al., 2015). In addition, the polymorphism was associated with increased risk for parental reporting of inattention.

Neurotransmission

Adenosine A2A Receptor (ADORA2A) Gene ADORA2A is a receptor located in neural, glial and endothelial cells in the CNS,

among others, to which the vasodilating nucleoside adenosine can bind (Cronstein, Naime, & Ostad, 1993). Activation of ADORA2A contributes to neurotoxicity by enhancing excitatory neurotransmitter release (e.g. glutamate), and by downregulation of the neuroprotective effect of ADORA1 (Fredholm, Chen, Cunha, Svenningsson, & Vaugeois, 2005).

Since the chemotherapeutic agent of MTX specifically leads to increased levels of adenosine, this genotype was only investigated in pediatric leukemia and lymphoma patients, both receiving MTX. Tsujimoto et al. (2016) assessed the effect of ADORA2A polymorphisms (Tsujimoto et al., 2016). The authors found that mainly in patients treated with lower cumulative MTX doses (<20 g/m^2), the ADORA2A rs2298383 CC genotype was associated with an increased risk of leukoencephalopathy. In the high cumulative dose group, this genotype showed only a tendency for an association with leukoencephalopathy, but this was not significant. This finding suggests that high MTX doses might attenuate the effect of ADORA2A.

Catechol-O-Methyltransferase (COMT) Gene COMT is an enzyme crucial for the metabolism of catecholamines, including dopamine. Its enzymatic activity is especially important for regulating dopamine levels in the prefrontal cortex. A substitution of valine by methionine on codon 158 (Val158Met) is associated with higher enzymatic activity, leading to lower dopamine availability. Dopamine is critically important for prefrontal-mediated cognitive functions (Bilder, Volavka, Lachman, & Grace, 2004; Meyer-Lindenberg et al., 2006; Park & Waldman, 2014; Savitz et al., 2006), which could be affected in cancer survivors, as they might require greater brain activation to maintain cognitive abilities (Ferguson, McDonald, Saykin, & Ahles, 2007; Silverman et al., 2007). Hence, prefrontal degradation in dopamine levels could lead to decreased resilience against neurotoxicity. We identified five studies which assessed the effect of COMT polymorphisms (Cole et al., 2015; Correa et al., 2016; Howarth et al., 2014; Krull et al., 2013a, b; Small et al., 2011), of which four reported significant findings.

With regard to pediatric research, two studies demonstrated lower working memory in COMT-Met homozygotes to score lower on working memory (Howarth et al., 2014) and parent-reported attention (Cole et al., 2015). Howarth et al. (2014) examined the relationship between COMT genotype and working memory in pediatric brain tumor survivors treated with conformal radiotherapy (Howarth et al., 2014). Contrary to their hypothesis (i.e. that COMT-Val carriers would perform worse), the authors reported decreased verbal working memory performance in Met homozygotes. Of note, this study excluded cognitively impaired patients (standard scores <70). However, Cole et al. (2015) similarly, observed a marginal association between Val158Met and parental reporting of attention and hyperactivity in pediatric leukemia survivors, with Met homozygotes performing worse (Cole et al., 2015). Such findings could be explained by assuming an inverted-U dose-response relationship between dopamine concentrations in the prefrontal cortex and cognitive performance (Vijayraghavan, Wang, Birnbaum, & Arnsten, 2007), in which deficient or excessive levels of dopamine would result in poorer performance. However, to confirm such hypothesis histological neurobiological investigations are required. The authors also stated that the COMT gene may not only be associated with inactivation of catecholamine neurotransmitters, but also with susceptibility to oxidative stress. According to this hypothesis, decreased COMT enzyme activity may lead to less protection against oxygen radicals (Miller, Selhub, & Joseph, 1996; Nappi & Vass, 1998), and as such increase susceptibility to treatment-related neurocognitive impairment. Still, conflicting results have been reported in pediatric studies, since Cole et al. (2015) and Krull et al. (2013a, 2013b) did not encounter associations between objective cognitive assessments and the COMT genotype in leukemia survivors Krull et al. (2013a, b).

In contrast to the findings in pediatric studies, suggesting Met-carriers to be at risk for cognitive decline, adult studies show COMT-carriers to have decreased performance. In a study by Small et al. (2011) in breast cancer survivors and a healthy control group, differences were found in favor of the COMT-Met homozygotes in attention, verbal fluency, and motor speed, compared to COMT-Val carriers (Small et al., 2011). Additionally, COMT-Val carriers treated with chemotherapy performed worse on attention tasks compared to healthy control Val-carriers. This suggests chemotherapy to elevate the risk of cognitive difficulties, in addition to the Val-allele. Correa et al. (2016) extended these findings with a study of adult brain tumor survivors who had completed cranial radiotherapy or chemotherapy (Correa et al., 2016). They reported that the COMT Val158Met polymorphism was associated with delayed verbal recall, with Val homozygotes again having lower scores compared to Met homozygotes. Moreover, they described ten additional COMT SNPs influencing attention, memory and executive functions. The observed difference between childhood and adult studies might demonstrate age-dependent neurotransmission and different consequent interactions. None were significantly associated with leukoencephalopathy.

Dystrobrevin-Binding Protein 1 (DTNBP1) Gene DTNBP1 is a protein interacting with glutaminergic, GABAergic, nicotinic, and dopaminergic neurotransmitter systems (Harrison & Weinberger, 2005; Tang et al., 2009), Hence, it is indirectly involved in regulation of neuroplasticity (Guo et al., 2009). The protein is widely expressed in the brain, with particularly the hippocampus and prefrontal cortex (Luciano et al., 2009).

Correa et al. found that DTNBP1 rs742106 was associated with verbal recognition memory, with carriers of the variant alleles showing worse performance in adult brain tumor patients (Correa et al., 2016). None of the DTNBP1 SNPs were significantly associated with white matter abnormalities on MRI.

Monoamine Oxidase a (MAO-A) Gene MAO-A is a mitochondrial enzyme which catalyzes deamination of (catechol-)amines (e.g. dopamine, norepinephrine and serotonin), critical for normal brain function (Nagatsu, 2004). Low enzyme activity is associated with increased norepinephrine, overactivation of the sympathetic nervous system (Gershon, Sherman, & Pintar, 1990), increased anxiety or physiological stress and attention problems (Ferreri, Lapp, & Peretti, 2011).

Two pediatric oncology studies assessed the effect of MAO-A polymorphisms (Cole et al., 2015; Krull et al., 2013a, b. Krull et al. (2013a, b) demonstrated increased reaction time variability in childhood leukemia survivors with the MAO-A 1460 T > C polymorphism (Krull et al., 2013a, b). Similarly, Cole et al. (2015) investigated neurocognitive assessments in childhood leukemia patients. However, these researchers did not encounter significant associations between the MAO-A and neurocognitive scores (Cole et al., 2015). In contrast to Krull et al. (2013a, b), this study did not acquire computerized tasks with high sensitivity for reaction times. Such sensitive measurements could be particularly be important to associate attention with the MAO-A gene.

Folate Metabolism Pathway Methotrexate (MTX) is an antifolate chemotherapeutic drug used widely in pediatric oncology for treating both hematologic (e.g. leukemia) and non-hematological (e.g. osteosarcoma) malignancies. MTX inhibits metabolism of folate during DNA synthesis (Finkelstein & Martin, 1986). We refer the reader to the study of Linnebank et al. (2009) for an overview of involved mechanisms, and consequent genes of interest (i.e. MTHFR, MS/MTR, Tc2, TSER). Prior studies have demonstrated acute MTX-related neurotoxicity or leukoencephalopathy (Kishi, Tanaka, & Ueda, 2000; Vezmar, Schüsseler, Becker, Bode, & Jaehde, 2009). MTX is known to increase homocysteine levels which can induce oxidative damage to neuronal tissue and to the vascular endothelium, and to excitotoxic glutamate analogs through further metabolism (Epstein, Lipton, & Rosenberg, 1994; Loscalzo, 1996; Quinn et al., 1997).

Methylenetetrahydrofolate Reductase (MTHFR) Gene Two SNPs in the MTHFR gene, C677T and A1298C, result in reduced MTHFR enzyme activity, and consequently increased neurotoxic homocysteine levels (Frosst et al., 1995; van der Put et al., 1998). We identified seven studies investigating MTHFR polymorphisms (Cole et al., 2015; Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2008; Krull et al., 2013a, b; Linnebank et al., 2005, 2009), of which four reported significant results.

Two pediatric leukemia studies demonstrated a link with parent-reported attention symptoms (Krull et al., 2008), shifting attention and global cognitive functioning (Kamdar et al., 2011). Krull et al. (2008) demonstrated higher levels of parent-reported attention-deficit/hyperactivity disorder (ADHD) symptoms, especially the inattentive subtype, in MTHFR 1298C carriers compared to 1298CC homozygotes. The 1298A > C genotype appeared to lead to a 7.4-fold increased risk for ADHD, while such increase was not significant for the 677C > T genotype (1.3-fold). Similarly, Kamdar et al. (2011) expanded these findings with neurocognitive assessments in leukemia survivors. They found that MTHFR 1298A > C carriers had a 3-fold increased risk of global cognitive impairment (defined as one standard score < 70 or 2 standard scores <80 on the DIVERGT screening battery) compared to non-carriers. More specifically, patients carrying this variant showed worse attention shifting performance. In addition to individual folate pathway polymorphisms, also combined risk haplotypes were investigated. Survivors with six or more adverse alleles in the investigated folate pathway variants consistently performed worse on attention and processing speed compared to those with less than six adverse alleles. The authors stated that these individuals may have prominent variation in folate or homocysteine levels making them more susceptible to neurocognitive deficits caused by MTX therapy. Such elevated risk in combined haplotypes, could explain the fact that studies which focused on the MTHFR 677C > T SNP only did not demonstrate significant associations with parent-reported ADHD (Krull et al., 2008), cognitive outcomes (Cole et al., 2015; Krajinovic et al., 2005; Krull et al., 2013a, b), nor with leukoencephalopathy (Tsujimoto et al., 2016), and that the previously mentioned associations between the MTHFR 1298A > C genotype and cognition also remain inconsistent (Cole et al., 2015; Krajinovic et al., 2005; Krull et al., 2013a, b).

In two adult primary CNS lymphoma studies by Linnebank et al. (2005, 2009), MRI scans were acquired before and after treatment with MTX-based multi-agent chemotherapy (Linnebank et al., 2005, 2009). In the first study, all patients received intraventricular treatment (Linnebank et al., 2005). This study demonstrated an association between the MTHFR 677C > T polymorphism and occurrence of white matter changes, albeit nonsignificant after correction for multiple testing. By contrast, a combined risk folate pathway haplotype, defined as presence of at least one of the genotypes MTHFR 677TT, MTR 2756AG/GG, or transcobalamin 2776GG, was a highly significant risk factor for leukoencephalopathy, with increased ratios of 4.7-fold. In their second study, the sample in the previous study was expanded with patients treated without intraventricular drug administration. Occurrence of leukoencephalopathy was now also independently predicted by the TT genotype of MTHFR 677C > T and by the AA genotype of MTHFR 1298A > C. Although the former association is in accordance with the hypothesis of elevated neurotoxic homocysteine levels and reduced SAM levels due to MTX, the latter association contradicts this hypothesis. However, both genotype variants are in linkage disequilibrium, with the 677 T allele

being linked to the 1298A allele (Linnebank et al., 2000). Therefore, it is possible that the 1298A allele is not directly associated with neurocognitive dysfunction, but is a surrogate marker for the tightly linked polymorphism 677 T which is responsible for the observed association.

Vitamin B12-Dependent Methionine Synthase (MS) or 5-Methyltetrahydrofolate-Homocysteine S-Methyltransferase (MTR) Gene Methionine synthase catalyzes remethylation of homocysteine to methionine, leading to decreased neurotoxic homocysteine levels (Stover, 2004). The MTR A2756G polymorphism has been suggested to affect the secondary structure of this protein, and as such can indirectly affect neurotoxicity (Leclerc et al., 1996; van der Put et al., 1997).

Three of the five studies examining the effect of this MTR polymorphism reported a significant association (Kamdar et al., 2011; Krajinovic et al., 2005; Krull et al., 2013a, b; Linnebank et al., 2005, 2009). Two pediatric leukemia studies demonstrated a link with general cognitive impairment (Kamdar et al., 2011) and with attentiveness (Krull et al., 2013a, b). Kamdar et al. (2011) demonstrated that childhood leukemia long-term survivors with the AA homozygotes of MTR 2756A > G had a 3.8-fold increased risk of global cognitive impairment (compared to AG/GG genotypes). Moreover, the AA genotype also appeared to be related to deficits in focused attention and processing speed. In contrast, discordant findings have been reported by Krull et al. (2013a, b). They found that childhood leukemia survivors with the MTR 2756AG/GG genotypes showed worse performance in attentiveness and response speed than the AA genotype. This inconsistency could be due to differences in attention assessments, that is, the Trail Making Test (Kamdar, 2011) versus the Continous Performance Test (Krull, 2013), respectively. In addition, these studies did not investigate the risk of a combined folate-related haplotype.

One adult lymphoma study by Linnebank et al. (2005) found that the MTR 2756A > G polymorphism was over-represented among patients with leukoencephalopathy after MTX treatment, albeit non-significant after correction for multiple testing (Linnebank et al., 2005). However, as previously mentioned, a combined folate-related risk haplotype was a highly significant predictor with a 4.7-fold risk for leukoencephalopathy.

Transcobalamin 2 (Tc2) Gene The Tc2 gene encodes transcobalamin 2, which acts as the main transporter of cobalamin (vitamin B12). The latter protein is necessary to remethylate methionine from homocysteine. The polymorphism Tc2 776C > G lowers the affinity of Tc2 to cobalamin, reducing such conversions and possibly leading to neurotoxicity (Von Castel-Dunwoody et al., 2005).

In two adult lymphoma studies by Linnebank et al. (2005, 2009), the effect of the Tc2 776C > G polymorphism on leukoencephalopathy was investigated (Linnebank et al., 2005, 2009). In the first study, the Tc2 776C > G polymorphism was over-represented among patients with leukoencephalopathy, though significance did not remain after correction for multiple testing (Linnebank et al., 2005). In the second (expanded) study, the GG genotype of Tc2 776C > G did significantly predict the occurrence of leukoencephalopathy (Linnebank et al., 2009). Still, a combined folate pathway risk haplotype also significantly increased the risk for leukoencephalopathy.

Thymidylate Synthase in the Form of Enhancer Region Repeats (TSER) Similar to MTHFR, Thymidylate synthase is an enzyme catalyzing intermediate conversions in the folate metabolism cycle (Stover, 2004). The promotor enhancer region of the TS gene can contain two or three 28-bp tandem repeat sequences, so-called 2R and 3R, respectively. TSER 3R/3R yields higher enzyme activity (Horie, Aiba, Oguro, Hojo, & Takeishi, 1995) and is associated with reduced folate and higher homocysteine levels (Trinh, Ong, Coetzee, Yu, & Laird, 2002).

We identified three studies in which TSER polymorphisms were examined (Cole et al., 2015; Kamdar et al., 2011; Linnebank et al., 2009). Only Kamdar et al. (2011) found a significant association, with pediatric leukemia survivors with TSER 2R/3R and 3R/3R genotypes exhibiting worse performance on shifting attention and processing speed, compared to those with the TSER 2R/2R genotypes. In contrast, no link was found with intelligence assessment subscales nor with parent-reported attention in leukemia patients (Cole et al., 2015), nor with leukoencephalopathy (Linnebank et al., 2009).

GWAS

The study by Bhojwani et al. (2014) was the only GWAS that has been carried out to date (Bhojwani et al., 2014). Serial brain MRI screening for leukoencephalopathy was performed in a large cohort of children with leukemia treated with high-dose MTX. The authors revealed polymorphisms in genes related to neurodevelopment (e.g., TRIO, SSPN, PRKG1, DKK2, ANK1, COL4A2, NTN1) with plausible roles in neurotoxicity. However, findings remained speculative since none of the SNPs reached significance. The lack of significance is probably due to the relatively limited sample size for a GWAS.

Discussion

The aim of this review was to summarize literature findings on the genetic modulation of cancer treatment-related neurocognitive impairment, and to highlight the importance of a neurodevelopmental perspective. This study indicates several polymorphisms across proposed pathophysiological pathways, that is, (1) neural plasticity and repair, (2) neuroinflammation and defenses against oxidative stress, (3)

neurotransmission, and (4) folate metabolism pathway, that may be involved in the complex polygenic susceptibility to cancer treatment-induced neurotoxicity throughout the lifespan.

With regard to pediatric research, each of the genotypes was investigated in leukemia patients, except for DTNB1. Although many of these genotypes were associated with neurocognitive outcomes (ApoE, GST, NOS3, SLCO2A1, ADORA2A, COMT, MAO-A, MTHFR, MTR, TSER) in leukemia patients, only the neuroinflammation-related genotypes (i.e. GST, NOS3, SLCO2A1) were consistently significant. Findings for the remaining genotypes appeared inconsistent, and only significant in case of specific, self-reported, attention-related assessments.

In contrast to the many pediatric investigations, fewer genotypes were investigated in adult cancer patients. These studies demonstrated the potential role of the ApoE and COMT genotypes in cognitive outcomes in breast cancer patients, of ApoE, BDNF, COMT, DTNB1 in cognitive outcomes in brain tumor patients, and of a combined folate pathway risk haplotype for leukoencephalopathy in lymphoma patients. In contrast to pediatric leukemia studies, genotypes were more frequently associated with memory than attention-related assessments.

One should note that many of the investigated genotypes (e.g. ApoE, BDNF, COMT, and MAO-A) were previously also associated with cognitive functioning, alterations in neuroimaging (Mattay & Goldberg, 2004), neuropsychiatric diseases and neurodegenerative disorders in general (Kennedy, Farrer, Andreasen, Mayeux, & St. George-Hyslop, 2003). In other words, these genotypes might relate to general neurocognitive development throughout the lifespan and age-dependent reserves (Lee, 2003), which could explain differences in vulnerability of patients. Each individual might have a unique threshold for tolerance of brain damage before clinical deficits are noted, depending on the age and genetic predisposition of the patient (Satz, 1993). Three of the reviewed studies included a healthy control group (Ahles et al., 2014; Brackett et al., 2012; Small et al., 2011), which suggested disadvantageous genotypes in healthy controls as well. To test whether such disadvantageous genotypes were more prevalent in cancer patients compared to controls, we performed post-hoc (chi-square) tests. However, these tests did not yield differences in frequencies of ApoE (Ahles et al., 2014), nor COMT polymorphisms (Small et al., 2011) between breast cancer patients and controls, nor in frequencies of GST polymorphisms between medulloblastoma patients and controls (Brackett et al., 2012). This finding could suggest that cancer patients are not more at risk for disadvantageous genotypes related to cognition in general.

The abovementioned genotypes were investigated given their link with neurodegeneration and neuroplasticity. In addition to degeneration-related genotypes (e.g. ApoE), genetic predispositions related to neurodevelopmental patterns during childhood could become particularly important in pediatric cancer patients. In this regard, genes related to cortical development (Thompson et al., 2001) and evolutionary genes (Dorus et al., 2004; Gilbert, Dobyns, & Lahn, 2005) will require more attention to in future studies compared to SNPs that were mainly investigated in adults, so far (e.g. ApoE).

In contrast to genotypes that are associated with neural plasticity, another group of genotypes interact with the administered therapies. For instance, GSTs catalyze detoxification of chemotherapeutic agents and free radicals, and folate pathway polymorphisms affect the metabolism of antifolate agents specifically, for example, methotrexate (Takimoto, 1996). Although the latter category of polymorphisms was discussed separately, we note that interactions between the metabolic, inflammatory and neurotransmission pathways are highly probable. Such pathways of induced neurotoxicity could be involved in both pediatric and adult patients. However, inflammation-related genotypes were only investigated in childhood cancer patients so far. Given that pediatric cancer patients receive treatment during major developmental changes, they may be particularly vulnerable to specific residual cognitive problems in contrast to the commonly held "plasticity" hypothesis. From a developmental perspective, frontal brain areas, particularly, which mainly develop during adolescence could be vulnerable to toxicity during childhood. Therefore, children might specifically be at risk for long-term attention-related problems. This hypothesis is concordant with the main findings of this review showing genetic associations with attention in leukemia patients. Failure in the acquisition of such core cognitive processes during critical periods, is expected to result in cumulative deficits. Given the increasing developmental demands with age, academic performance, job success, social functioning and mental health may be affected over time (Mulhern & Palmer, 2003).

On the other hand, adult cancer patients could be more at risk for accelerated ageing and neurodegenerative processes (Billiet et al., 2015; Lange et al., 2014). Ageing could, in this case, lead not only to attention-related problems, but also to memory problems, for example, due to hippocampal atrophy (Kesler et al., 2013a, b). The fact that adult studies mainly revealed a link between specific genotypes (e.g. ApoE) and memory assessments, seems to be in line with the hypothesis of age-dependent neurotoxic effects. Not only the genetic effects on cognitive outcomes seem to be age-related. Also cognitively 'impaired' scores across the included cancer studies seem age-related. In this review, only three studies demonstrated mean cognitive scores of patients that reached a clinical cut-off (1SD). Pediatric medulloblastoma patients with GSTM1 or GSTT1 null genotype obtained intelligence scores <85 (Barahmani et al., 2009). Similarly, adult brain tumor patients carrying the ApoE4 allele obtained lower verbal memory and shifting attention scores which deviated more than one standard deviation (Correa et al., 2014a, b). In

contrast to these two CNS tumor studies, the number of 'impaired' patients is less in studies of non-CNS tumor patients (Small et al., 2011). Consistent with this inference, the majority of the included non-CNS tumor studies in this review reported mean scores within the normal range. However, Krull et al. (2013a, b) still demonstrated reduced (i.e. <1SD) mean scores on attentiveness and response speed in leukemia patients. In conclusion, specific cognitive functions might be mostly affected within certain age ranges.

Pre-inclusion neurocognitive screening instruments are advised in future studies in order to clarify recruitment of impaired patients, and discover individual vulnerability factors. Once genetic predictions of cognitive status as well as normal brain development and ageing become well-established, treatments can evolve towards genotype-tailored regimens. For instance, more fractionated, lower doses, or less neurotoxic chemotherapeutic agents could be preferred in children at risk for neurodevelopmental delay and adults at risk for degeneration.

Considering the low number of studies and discordant findings, it remains difficult to draw definite conclusions. The included studies were heterogeneous with respect to study design, sample size, ethnicity, cancer types, age at diagnosis, treatment regimens, assessment techniques (i.e. neuroimaging vs. neurocognitive evaluation; objective performance vs. subjective self-report measures) and assessed cognitive domains (i.e. global vs. specific functioning), and post-treatment intervals. A first shortcoming concerns the lack of longitudinal information. Longitudinal neurocognitive assessments were only available in three studies. The ideal research design to understand the effect of cancer treatment on neurocognitive developmental patterns, would be a longitudinal design with baseline assessments and neuroimaging. However, many studies did not include pre-treatment data, probably due to practical issues inherent to the clinical setting. Nevertheless, pre-treatment evaluation is recommended to detect changes related to cancer treatment, not to pre-existing differences. Secondly, since treatment-induced dysfunction can sometimes be subtle, post-treatment scores are often still within the normal range, although the patient has deteriorated. Such subtle changes cannot be detected without pre-treatment evaluation or sensitive cognitive (e.g. computerized attention) tasks, leading to false-negative findings. In addition, patients are ideally compared to age- and gender-matched peer control participants or siblings, who undergo the same assessments within the same timeframe. This is important since genetic predispositions could not only be main effects, but also interact with cancer or treatment effects, which is only possible to identify by including control groups. The three studies including healthy controls mainly focused on main effects within patient groups, but we refer the reader to these studies to appreciate specific between-group effects in more detail, namely, ApoE and COMT in breast cancer (Ahles et al., 2014; Small et al., 2011), and GST in medulloblastoma (Brackett et al., 2012). Given the heterogeneity in treatment protocols between cancer patients (i.e. according to international clinical trials), protocols or chemotherapeutic agent doses should be compared or controlled for.

Thirdly, study samples were often relatively small. Many studies were not designed with an a priori sample size calculation. Ideally, to ensure sufficient statistical power in genetic association studies, sample sizes should be determined a priori by the minor allele frequency of the investigated variant and its effect size. Furthermore, some inconsistent findings (e.g. MTHFR in leukemia patients) suggest the occurrence of treatment-related neurocognitive impairment to rather reflect an age-dependent polygenic trait, with cumulative risk determined by multiple risk alleles with low-to-medium effect sizes. In this regard, two studies showed higher risk for ADHD-related inattention symptoms (Krull et al., 2008) and leukoencephalopathy (Linnebank et al., 2005) in case of combined folate-metabolism-related risk haplotype. Therefore, the current approaches to associate SNPs with behavior and imaging probably requires more integrative statistical approaches. The two mentioned studies already implemented analyses of combined haplotypes. However, ideally genetic (regulatory) networks should receive more attention in future studies, as gene expression is appreciated to be dynamic and relying on interacting regulatory drivers (Schlauch, Glass, Hersh, Silverman, & Quackenbush, 2017).

In addition, reliable detection will require larger sample sizes than most of the reviewed studies (Jorgensen & Williamson, 2008; Ross, Anand, Joseph, & Paré, 2012). Hence, validation of current findings in sufficiently large cancer cohorts, requiring large international consortia, will be necessary for clinical implementation in the future.

Furthermore, timing of assessments varied widely between studies. We selected six months post-consolidation of treatment as the cut-off to ensure that sufficient time had elapsed for neurocognitive assessments. However, this may still not reflect patterns seen in long-term survivors. In this regard, acute leukoencephalopathy was included, since recent evidence was found for long-term cognitive decline in case of such acute neural damage (Cheung et al., 2018). Hence, we suggest future research should incorporate post-treatment neuroimaging and investigate the link with long-term cognitive outcomes throughout the lifespan. Moreover, the included studies were heterogeneous with respect to assessment methods. A standardized, uniform approach to these two key features, that is, timing and assessment tools, will be critical in constructing the aforementioned international consortia. There has already been some preliminary consensus on a core set of neuropsychological tests with relevance to cancer and its treatment (Tannock, Ahles, Ganz, & Van Dam, 2004; Wefel et al., 2011). Considering that neuroimaging studies have provided important neurobiological evidence for the

impact of treatment on neurocognition, a multifaceted approach that integrates both neuropsychological assessments and neuroimaging is essential. In the reviewed studies that investigated leukoencephalopathy as the outcome of interest, T2-weighted MRI and FLAIR sequences were typically used. However, more advanced MRI techniques such as functional MRI, diffusion-weighted imaging (DWI), spectroscopy (MRS) and anatomical volumetric studies, may currently provide greater sensitivity to treatment-related CNS changes (Deprez et al., 2018). Spectroscopy could specifically add information regarding underlying metabolic and inflammatory changes (S. R. Kesler et al., 2013a, b; Stouten-Kemperman et al., 2014), while other techniques (i.e. fMRI, DWI) enable researchers to estimate structural and functional brain networks (i.e. so-called 'connectomes'). Given that neuroscientific research increasingly acknowledges the importance of interactions between brain areas, investigations of the 'organization' or 'topology' of the brain and its link with genetic polymorphisms may lead to progress in exploring neural damage to networks and vulnerable brain areas (Aerts, Fias, Caeyenberghs, & Marinazzo, 2016; Stam, 2014).

Another important consideration is that most of the included studies used a targeted approach, focusing on specific SNP candidates, which are believed to play a role in treatment-related neurotoxicity. As discussed previously, the occurrence of treatment-related neurocognitive impairment rather reflects a polygenic and age-dependent trait, which requires broader approaches to address combined risk haplotypes, for instance by performing GWASs. In contrast to targeted approaches, GWASs provide an 'agnostic' approach in which no a priori biological hypothesis is needed so that unsuspected but important novel genes could be identified. Despite substantial advantages, very large cohorts are required to reach sufficient power in such analyses. This, once again, emphasizes the need for international collaborations. However, neurocognitive functioning cannot be predicted by genetic predisposition only. Next-generation sequencing and modern bioinformatics provide exploratory investigations towards epigenetic effects and the dynamic genome. Furthermore, interactions between genetic predisposition and neuro-hormonal processes will become important to address in the near future. None of the studies investigated interactions between genes, treatments and age. With regard to affected neurotransmission in adult cancer patients, interactions between the ApoE genotype and nicotine could suggest modification of cholinergic transmission. Similarly, in children, stress-related situations, which is indisputably the case in childhood cancer, and steroid hormones could also modify neurophysiological messengers as well as gene transcription (Hunter, Gagnidze, McEwen, & Pfaff, 2014). Therefore, integrative approaches such as gene regulatory factors and epigenetic investigations, are highly recommended to address pathophysiological pathways and dynamic regulation of genotypes of interest.

Conclusion

Considering the recommendations, we believe that further genetic research holds great promise for minimizing adverse neurodevelopmental and neurodegenerative outcomes in cancer patients by enabling (1) prognostication of neurocognition, followed by risk-adapted, genotype-tailored treatments and prophylactic interventions early in development or in degenerative cascades and (2) identification of intervention targets to protect the nervous system. This strategy potentially would enhance the therapeutic index for curative therapy and improve cancer survivor's quality of life. Large scale, collaborative GWAS and epigenetic investigations, integrating longitudinal neurocognitive assessments and advanced neuroimaging techniques will become highly important. However, as the etiology of cognitive impairment in cancer survivors is likely multifactorial, an important challenge will be to integrate genetic information with other epigenetic risk factors.

Compliance with Ethical Standards

Conflict of Interest None.

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