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Neurodevelopmental consequences of pediatric cancer and its treatment: applying an early adversity framework to understanding cognitive, behavioral, and emotional outcomes

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Abstract

Today, children are surviving pediatric cancer at unprecedented rates, making it one of modern medicine's true success stories. However, we are increasingly becoming aware of several deleterious effects of cancer and the subsequent "cure" that extend beyond physical sequelae. Indeed, survivors of childhood cancer commonly report cognitive, emotional, and psychological difficulties, including attentional difficulties, anxiety, and posttraumatic stress symptoms (PTSS). Cognitive late- and long-term effects have been largely attributed to neurotoxic effects of cancer treatments (e.g., chemotherapy, cranial irradiation, surgery) on brain development. The role of *childhood adversity* in pediatric cancer – namely, the presence of a life-threatening disease and endurance of invasive medical procedures – has been largely ignored in the existing neuroscientific literature, despite compelling research by our group and others showing that exposure to more commonly studied adverse childhood experiences (i.e., domestic and community violence, physical, sexual, and emotional abuse) strongly imprints on neural development. While these adverse childhood experiences are different in many ways from the experience of childhood cancer (e.g., context, nature, source), they do share a common element of exposure to threat (i.e., threat to life or physical integrity). Therefore, we argue that the double hit of early threat and cancer

treatments likely alters neural development, and ultimately, cognitive, behavioral, and emotional outcomes. In this paper, we (1) review the existing neuroimaging research on child, adolescent, and adult survivors of childhood cancer, (2) summarize gaps in our current understanding, (3) propose a novel neurobiological framework that characterizes childhood cancer as a type of childhood adversity, particularly a form of early threat, focusing on development of the hippocampus and the salience and emotion network (SEN), and (4) outline future directions for research.

Keywords

Childhood cancer; pediatric oncology; leukemia; brain tumor; brain

Introduction

Although cancer remains the leading disease-related cause of death among US children, recent advances in treatment for pediatric cancer have improved the outlook for many children with cancer. Today, nearly 90% of children diagnosed with cancer are surviving at least five years after diagnosis, and more than 70% will survive ten years - making it one of modern medicine's true success stories (Howlader et al. 2016). However, survivors of childhood cancer frequently experience "late" and long-term effects associated with the disease and its intensive treatment, including chronic medical conditions and impairment in level of cognitive, behavioral, and emotional functioning (Bitsko et al. 2016; Anderson & Kunin-Batson 2009; Marcoux et al. 2016; Ehrhardt n.d.; Pogany et al. 2006; see review by Stein et al. 2008). Recent cognitive and developmental neuroscience research indicates that these late effects are due, in part, to injurious effects of therapeutic intervention (e.g., chemotherapy, cranial irradiation, surgery) during cancer treatment on the developing brain (Cheung & Krull 2015; Butler & Haser 2006; Ashford et al. 2010; Cheung et al. 2016). Here, we contend that the effects of pediatric cancer as an *adverse childhood experience* are also important to consider when evaluating psychological and neurodevelopmental outcomes. Childhood adversity is defined as an experience that is likely to require significant psychological, social, or neurobiological adaptation by the average child and that represents a deviation from the expectable (safe) rearing environment (McLaughlin 2016). The role of childhood adversity in pediatric cancer – namely, the presence of a life-threatening disease and endurance of invasive medical procedures – has been largely ignored in the neuroscientific literature. This is true despite compelling research by our group and others showing that other adverse childhood experiences, which involve shared elements of life threat and threat to physical integrity (e.g., violence, abuse) – but are also disparate in many important ways (e.g., context, source of threat, chronicity, onset, long-term debilitation) – strongly imprint on neural development. Moreover, these neuro developmental changes alter core cognitive and affective processes that are thought to increase risk for psychological issues and disorders (see reviews by Thomason & Marusak 2016; Teicher & Samson 2016). Lack of consideration of the additional and unique role of early threat constitutes a critical barrier to identifying pathways through which pediatric cancer impacts neural development, and ultimately, psychological outcomes.

Pediatric cancer patients and their families face enormous adversity that begins at the time of diagnosis. Cancer diagnosis is surprising and life threatening, forcing children and families to re-organize their lives and relationships. At the same time, families are confronted with the tremendous burden of understanding the disease and facing the possibility of the child's death at a young age. In addition, the procedures and treatments associated with pediatric cancer care are invasive, unfamiliar, and arduous (e.g., lumbar punctures, bone marrow aspirations, and port starts), and often cause significant physical side effects. Children frequently do not grasp why these recurrent body intrusions, pain, and hospitalizations are necessary and both parents and children often describe the stress, nausea, and fatigue associated with treatment to be more stressful than the disease itself (Hedström et al. 2003). At the same time, there may be deaths of other children known to the patient and family. Together, these take an immense emotional toll on children and families, as coping and financial resources are strained. For children who survive cancer, stress and adversity do not end after the child crosses the "finish line" and treatment concludes. The transition into survivorship brings its own set of challenges as families begin to readjust to home and family life, re-acclimate to school and social settings, and deal with physical limitations and chronic pain (Hobbie et al. 2010). Concerns about safety persist throughout the lifespan, due to emergence of various late and long-term effects and the risk of relapse or second malignancies. Childhood cancer survivors therefore require ongoing medical surveillance, which can induce hypervigilance and chronic worry about physical symptoms. Overall, the burden of receiving a life-threatening diagnosis, concerns about safety, disruptions of the family system and members, and painful treatments and medical procedures associated with cancer care constitute a significant deviation from the expectable safe rearing environment, and can be conceptualized as a form of adverse childhood experience (see Alderfer & Kazak 2006; Trentacosta et al. 2016; F. W. Harper et al. 2014b, 2015).

Pediatric cancer patients and survivors frequently experience cognitive and affective dysfunction, months, years, and even decades after cancer. Despite replacement of cranial irradiation (with chemotherapy) in many contemporary treatment protocols, estimated rates of cognitive dysfunction in survivors of childhood cancer remain as high as 67% for attentional deficits, and 3–28% for deficits in other cognitive domains (Conklin et al. 2012a, b), including executive functioning, intelligence quotient (IQ), memory, processing speed, and visual-motor integration (for a review, see Castellino et al. 2014). Emotion-related psychological problems, including anxiety, depression, and posttraumatic stress symptoms (PTSS), are frequently experienced in a subset of children (Oancea et al. 2014; Zeltzer et al. 2009; Kunin-Batson et al. 2016; Kazak et al. 2004; Price et al. 2016; Landolt et al. 2012). Of note, a recent systematic review suggests that anxiety is a relevant but understudied psychosocial outcome among pediatric cancer survivors (McDonnell et al. 2017). Estimated life-time rates of posttraumatic stress disorder (PTSD) among survivors range from 20 to 35% (see review by Bruce 2006) - nearly double what is observed in the general population and may even exceed rates reported in some military Veteran populations (National Center for PTSD 2016). These psychological problems are a major source of compromised quality of life among childhood cancer patients and survivors, and disrupt daily life, impair social functioning and academic performance, and may even increase disease morbidity, mortality, and healthcare costs by reducing children's adherence to medical procedures.

Compelling research over the past several decades has shown that exposure to other forms of childhood adversity - including violence (e.g., domestic, community), abuse (e.g., physical or sexual abuse), and neglect - dramatically increases risk for cognitive, behavioral, and emotional problems, and for virtually all commonly occurring psychiatric disorders (e.g., anxiety, depression, PTSD; Kessler et al. 2010; Felitti et al. 1998). Although the circumstances and nature of these experiences differs dramatically from the childhood cancer experience, an early adversity framework provides a useful starting point for understanding how the developing brain adapts to adversity and early threat exposure during childhood. Indeed, similar to observations in cancer survivors, psychological issues or disorders may emerge insidiously years or even decades after exposure to other forms of childhood adversity, which is thought to reflect a latent biological vulnerability (Caspi et al. 2014; Keyes et al. 2012). Neuroscientific research suggests that this latent vulnerability is mediated by adversity-related changes in brain structure and function, which are evident even in those who do not present with psychological problems, and are remarkably similar to neural changes in clinical groups with adversity-related disorders (e.g., depression, anxiety, PTSD; see reviews by Thomason & Marusak 2016; Teicher & Samson 2016). Adversity-related changes in the brain are thought to underlie alterations in core cognitive and affective processes (e.g., elevated threat processing, decreased executive control) that increase risk for cognitive, behavioral, and emotional problems in some youth (McCrory et al. 2017).

Given the strong and pervasive link between threat-related childhood adversity and a range of negative psychological outcomes, as well as the impact of early threat on neural development (see reviews by Thomason & Marusak 2016; Teicher & Samson 2016), we argue that research into the neurodevelopmental consequences of pediatric cancer should consider the joint impact of early threat and cancer treatments (Fig. 1). It is likely that the double hit of early threat and therapeutic intervention imprints strongly on brain development, and may thus contribute to a range of cognitive, behavioral, emotional, and also physical consequences. We assert that childhood cancer is another, largely understudied form of childhood adversity and brain injury. As we will discuss below, the majority (60%) of the existing studies on brain structure or function in childhood cancer survivors have been in patients and survivors of central nervous system (CNS) tumors (e.g., medulloblastoma, ependymoma), the second most common form of childhood cancer. This focus is likely due to their central location within the CNS and the direct effects of treatment (e.g., cranial irradiation) on brain functioning. We propose taking a broader view beyond the effects of cancer treatment itself on the brain in CNS cancer and additionally consider the cancer experience, regardless of type of cancer, as an adverse event. For example, acute lymphoblastic leukemia (ALL), the most common type of childhood cancer, is a non-CNS cancer that is now conventionally treated with an intensive chemotherapy-only approach, which may have a less direct effect on the brain than cranial irradiation. Yet, ALL patients and families undoubtedly experience enormous adversity, and several cognitive, behavioral, and emotional late effects are reported (Trentacosta et al. 2016; Harper et al. 2014b; Peterson et al. 2014; Harper et al. 2015; Cheung & Krull 2015). Characterizing the relationships among these challenges and underlying neurobiological processes should provide new insights into mechanisms of risk and novel avenues for intervention.

The notion that childhood cancer is an adverse and potentially traumatic experience is not new (e.g., Stuber et al. 1998; Bruce 2006; Kazak et al. 2005). Although many children report at least some symptoms of anxiety, depression, or PTSS (Bitsko et al. 2016), pediatric cancer survivors generally function well despite the enormous challenge and threat that they face (Eiser et al. 2000). However, research is needed to identify pathways through which childhood cancer impacts neural development, and ultimately, psychological outcomes. Lack of consideration of the additional role of early threat exposure constitutes a critical barrier to identifying potential drivers of neurodevelopmental change. As we will demonstrate later in our review of the literature, following these early experiences, individuals experience the world with a fundamentally altered nervous system.

Organizations such as the National Institutes of Health (NIH), American Cancer Society (ACS), and Centers for Disease Control and Prevention (CDC) have emphasized the importance of research on cancer outcomes. In their seminal report in 2006, the Institute of Medicine and National Research Council identified survivorship issues as a key research priority (Institute of Medicine and National Research Council, 2006). We add to this by suggesting that the “cure” for childhood cancer should not only consider psychological wellbeing, but also neurodevelopmental consequences. Second, given that neurodevelopmental alterations as well as psychological issues and disorders frequently begin in childhood and adolescence (Kessler et al. 2005), this further emphasizes a focus on *prevention*. Specifically, interventions may be initiated during or after treatment to correct aberrant neurodevelopmental processes, before frank psychological problems emerge and become chronic.

Early intervention will be even more critical as this expanding population ages. Indeed, the number of pediatric cancer survivors will continue to grow, due to advances in treatments, increasing incidence, and the fact that survivors are living longer than ever before (Howlader et al. 2016). It is estimated that there will be nearly 500,000 survivors of pediatric cancer in the US by the year 2020 (Robison & Hudson 2014). Medical and research communities are challenged to meet this growing population with empirically-based services and interventions to address survivors’ psychological needs. Research into neurodevelopmental and psychological consequences of pediatric cancer should aid the development and more judicious application of targeted early interventions to improve life during and after children’s treatments for cancer.

In this paper, we (1) review the existing, yet limited, human neuroimaging research in child, adolescent, and adult survivors of childhood cancer, (2) summarize gaps in our current understanding, (3) advance a neurodevelopmental model of childhood adversity, and in particular, early threat exposures, into the area of pediatric cancer, and (4) present future directions for research. Of note, we do not discount the cognitive effects of pediatric cancer, and refer the reader to comprehensive reviews in this area (Cheung & Krull 2015; Wolfe et al. 2012; Robinson et al. 2013; Castellino et al. 2014). In addition, neurocognitive dysfunction is also observed in adults treated for cancer (Correa & Ahles 2008; Jean-Pierre & McDonald 2016; O’Farrell et al. 2013), which is not necessarily through a developmental mechanism. However, some have noted that neurocognitive dysfunction complicating pediatric cancer appears to be more frequent and severe than “chemo brain” in adults (for a

review, see Castellino et al. 2014), which may be due to the sensitivity of brain systems to insults during development. Here, it is our hope that widening the lens to consider the joint impact of early threat and therapeutic intervention on cognitive, behavioral, and emotional outcomes will offer an integrative neurobiological framework for how early cancer affects the developing brain, and provide more comprehensive understanding of late and long-term effects in survivors of childhood cancer. We propose such a framework here.

Neuroimaging studies in child and adolescent cancer patients and survivors

We performed a literature review using PubMed and Google Scholar to identify neuroimaging studies that include child or adolescent patients or survivors of childhood cancer, using various combinations of the following search terms: “brain”, “MRI”, “fMRI”, “childhood cancer”, “adult survivors”, “neuroimaging”, “gray matter”, “white matter”, “cortical thickness”, “leukoencephalopathy”, “leukodystrophy”, “pediatric cancer”, “leukemia”, “chemotherapy”, “radiation”, “posterior fossa”, “medulloblastoma”, “neuroblastoma”, “brain tumor”. Reviewed studies are limited to structural or functional magnetic resonance imaging (fMRI) methods, but not restricted in the type of child or adolescent cancer (i.e., diagnosis prior to age 18). Neuroimaging studies related to pre-surgical planning or differential diagnosis (e.g., low- vs high-grade brain tumors) were not reviewed.

The literature search identified 65 studies that examined brain structure or function in child or adolescent cancer patients/survivors (see Table 1). The majority (83%) of studies examined structural neurobiological changes during or following children’s treatments for cancer, including variation in regional gray matter volume or cortical thickness, as measured by structural MRI, or white matter macrostructure (e.g., fiber density, axonal diameter, and myelination), as measured by diffusion tensor imaging (DTI) MRI. Two studies used perfusion MRI (such as arterial spin labelling, ASL), which measures relative changes in cerebral blood volume and blood flow without the need for contrast administration (Hartkamp et al. 2013). Ten pediatric neuroimaging studies used blood-oxygen level-dependent (BOLD) fMRI to measure brain function via the hemodynamic response, with nine measuring fMRI response during a neuropsychological task (e.g., working memory), and one measuring resting-state functional connectivity (rsFC). RsFC measures spontaneous fluctuations in the BOLD signal, and correlations in activity are thought to reflect the baseline functional intrinsic architecture of the brain (Fox & Raichle 2007). Connectivity patterns observed during the resting-state have been shown to predict individual differences in fMRI response across a wide range of neuropsychological tasks (Tavor et al. 2016). The number of patients/survivors ranged widely in studies, with 2–197 for structural imaging studies, and 8–218 for functional neuroimaging studies. Forty-five percent of studies included patients with leukemia, and 63% with brain tumors, particularly in the posterior fossa, the most common site of pediatric CNS tumors. The majority (69%) of neuroimaging studies linked neurobiological changes to cognitive outcome measures (e.g., IQ, working memory, processing speed), and only five studies linked neurobiological changes to

emotional outcomes (e.g., internalizing symptoms, emotional adjustment) or quality of life (see Table 1).

Structural or diffusion MRI studies

The majority (63%) of the 55 structural MRI or DTI studies examined CNS tumor patients and survivors, and the remaining 37% examined ALL survivors exclusively. Several studies in brain tumor patients and survivors identify damage to brain areas following surgical tumor resection, for e.g., the cerebellum. Given the critical role of the cerebellum in motor control and balance, several studies have linked cerebellar lesions to deficits in motor functioning (Küper et al. 2013; Khajuria et al. 2015; Konczak et al. 2005). However, the cerebellum is increasingly recognized for its role in high-order non-motor processes such as learning, memory, and emotion, and several studies link damage in particular locations with neurocognitive difficulties (i.e., left hemisphere lobule VIII; Kirschen et al. 2008) and parent-reported affect dysregulation (i.e., vermis; Levisohn et al. 2000).

Several studies also suggest that brain tumor and its resection disrupt white matter pathways connecting cerebellum with prefrontal, superior temporal, and limbic regions, and reduced white matter is frequently associated with poorer neurocognitive functioning (e.g., processing speed, IQ, memory). Reductions in white matter volume are also reported in five studies of young ALL survivors (Kesler et al. 2010; Ashford et al. 2010; ElAlfy et al. 2014; Cheung et al. 2016; Aukema et al. 2009), including in the corpus callosum, striatum, and thalamus, and these reductions have also been linked to deficits in cognitive functioning (see Table 1). Several studies report greater reductions in white matter volume or indicators of macrostructure with younger age at treatment, greater time since treatment, and greater CNS treatment intensity (see Table 1). Taken together, existing studies indicate white matter damage in children and adolescents, irrespective of cancer type or treatment received. However, there is some evidence suggesting that degree of white matter damage is more severe following cranial radiation relative to chemotherapy only, and in brain tumor survivors relative to ALL survivors, potentially because radiation is a more primary component of treatment for childhood CNS tumors relative to ALL. The relation between white matter integrity and neurocognitive functioning has prompted several investigators to assert that altered white matter integrity may serve as a biomarker for identifying risk for neurocognitive impairment. The cause of injury to white matter is unknown, but may involve treatment-induced damage to newly synthesized and less stable myelin, glial cells, oligodendrocyte precursors, and microvascular structure (Hopewell et al. 1993; Krull et al. 2013a, b; Monje & Dietrich 2012), and/or microglial activation associated with oxidative and nitrosative stress (Lull & Block 2010).

In addition, many patients develop chronic or transient leukoencephalopathy (i.e., white matter lesions) during treatment, a more overt marker of white matter neurotoxicity. In fact, as many as 80% of patients treated for ALL without irradiation may develop leukoencephalopathy (Reddick et al. 2005a, b), leaving them at high risk for severe neurologic morbidity. A recent longitudinal neuroimaging study demonstrates that nearly a quarter of children treated for ALL developed *asymptomatic* leukoencephalopathy during active chemotherapy (Bhojwani et al. 2014), and these children displayed more parent-rated

cognitive problems (i.e., poorer working memory [capacity to manipulate information in one's mind], organization [ability to organize information to achieve a goal or organize one's environment], and initiation, [ability to get started on activities]) at follow-up more than 5 years after diagnosis than did survivors who did not display leukoencephalopathy (Cheung et al. 2016). In addition, leukoencephalopathy during chemotherapy treatment predicted reduced white matter integrity in the frontostriatal tract at follow-up, suggesting further white matter damage (Cheung et al. 2016). These findings demonstrate that changes in the brain, even in the absence of current symptoms or overt behavioral changes, can predict later neurocognitive outcomes (e.g., executive functioning).

Several studies examine gray matter structure. Three studies report reductions in hippocampal volume following treatment of brain tumor or ALL (see Fig. 2a; Riggs et al. 2014; Nagel et al. 2004; Genshaft et al. 2013), which corresponded with poorer performance on hippocampal-dependent memory tasks (Genshaft et al. 2013; Riggs et al. 2014). In these studies, hippocampal damage was largely attributed to cancer treatment-induced inhibition of hippocampal neurogenesis. However, one study comparing 10 ALL survivors (ages 7–14) with 10 matched controls failed to find significant differences in hippocampal volume, or in long-term memory (Hill et al. 2004), which may suggest significant inter-individual variability in hippocampal damage, or may be related to specific study characteristics (e.g., patients, sample size, methodology for measuring hippocampus). Riggs et al. (2014) also found reductions in indicators of white matter macrostructure among brain tumor survivors within the uncinate fasciculus, the major white matter pathway connecting hippocampus and amygdala with frontal regions, including the prefrontal cortex (PFC) and anterior cingulate cortex (ACC). The uncinate fasciculus plays a significant role in the development and support of memory processes (Ghetti & Bunge 2012), and shows a protracted maturational course into adulthood (Simmonds et al. 2014). Thus, early cancer-related disruptions to this pathway may underlie deficits in later-emerging processes that rely on interactions between temporal and prefrontal regions (e.g., memory, emotion regulation).

In addition to alterations in the hippocampus, Genshaft et al. (2013) reported reduced volumes of the amygdala, thalamus, and nucleus accumbens in ALL survivors relative to controls. These regions are considered part of the “salience and emotion network” (SEN), a large-scale neurocognitive network involved in attentional awareness, emotion processing, and regulation (Seeley et al. 2007). Altered organization of large-scale structural brain networks has been reported in two studies. Hosseini et al. (2012) applied graph theoretical analysis to structural MRI data, and observed a significant reduction in small-world characteristics (a measure of information processing efficiency) in young ALL survivors relative to controls, consistent with widespread neurobiological injury. Similarly, Kesler et al. (2016) found lower small-worldness in young ALL survivors relative to controls, using graph theoretical analysis and DTI data. In this study, regional differences in nodal clustering was observed in several regions of the SEN, including amygdala and insula, and also hippocampus (see Fig. 2b; Kesler et al. 2016). Together, these findings suggest more widespread alterations in brain structure following pediatric cancer, even without CNS disease or cranial radiation therapy.

Functional MRI studies

Of the 10 existing task-based fMRI studies (see Table 1), five examined neural functioning during a working memory task (Robinson et al. 2010; Conklin et al. 2015; Wolfe et al. 2013; Robinson et al. 2014; Robinson et al. 2015), two during an attention task (continuous performance task, “attention network task”; Krull et al. 2016; Zou et al. 2012), one during a visual stimulation task (Zou et al. 2005), and one during several fMRI tasks probing reading-related neural activation (Zou et al. 2016). Four studies (Zou et al. 2016; Robinson et al. 2014; Robinson et al. 2015; Wolfe et al. 2013) examined brain tumor patients/survivors exclusively, two (Krull et al. 2016; Robinson et al. 2010) examined ALL survivors exclusively, and three examined a mix of ALL and CNS tumor survivors (Zou et al. 2012; Zou et al. 2005; Conklin et al. 2015). The three studies by Robinson et al. (2010, 2014, 2015) demonstrate a similar pattern of increased neural response in areas of the PFC, considered part of the “central executive network” (CEN), and the ACC (a SEN region) during an n-back working memory paradigm among survivors of brain tumor or ALL relative to healthy controls (see Fig. 3a). Given the critical role of PFC and ACC in working memory and executive functioning more broadly, the authors propose that greater neural response in these regions reflects a compensatory neural mechanism in survivors that helps to maintain behavioral performance following brain insult. In line with this interpretation, survivors of ALL did not differ in behavioral performance from controls (Robinson et al. 2010). However, pediatric brain tumor survivors performed significantly less accurately than controls, suggesting an ineffective compensatory neural mechanism in this group (Robinson et al. 2014). In fact, higher response in ACC was associated with poorer task accuracy, suggesting that increased engagement of the SEN did not facilitate better performance (Robinson et al. 2014). Together, these findings are interesting and important because they uncover similar neurobehavioral changes in a sample of brain tumor survivors, treated primarily (71%) with surgical resection and cranial radiation (without chemotherapy), and a sample of ALL survivors, treated exclusively with chemotherapy (without surgery and cranial radiation). Further, Robinson and colleagues reported that chemotherapy and radiation dosage were not associated with behavioral performance during the working memory task (Robinson et al. 2014). Altogether, these findings raise the possibility that specific brain regions, particularly those showing a protracted developmental trajectory (e.g., PFC, ACC; Gogtay & Thompson 2010; Tiemeier et al. 2010) are sensitive to various CNS-directed cancer therapies during childhood (e.g., radiation therapy, chemotherapy), or, that there are shared aspects of the childhood cancer experience (e.g., adversity) that may imprint on brain development. As we outlined in the beginning, these are not mutually exclusive.

Robinson et al.’s 2014 study was also the only fMRI study that linked measures of neural function with measures of psychosocial or emotional wellbeing. Specifically, the authors reported elevated psychosocial and behavioral/emotional difficulties (e.g., reduced self- and parent-reports of social competence) in survivors relative to controls and normative data, and that, both within and across groups, children who showed higher PFC response also reported better psychological functioning (i.e. lower symptoms of anxiety and depression). Further, self-reported engagement of secondary control coping strategies to social stress (i.e., acceptance, cognitive restructuring, positive thinking, distraction) accounted for a significant

portion of the association between brain activation and psychological functioning, suggesting that engagement of the PFC is adaptive in this context. The link between psychological wellbeing and PFC response during working memory is not surprising given that areas of the PFC are also implicated in socioemotional processes (Etkin et al. 2011). These data are important because they are the first to link altered neural functioning with psychosocial and emotional wellbeing in survivors. As we will discuss later, it will be critical to expand our understanding of neurobehavioral correlates of psychological and emotional wellbeing in young survivors, and interrogate proximal processes that may be relevant for social and emotional functioning (e.g., emotion regulation, fear- and extinction-learning).

A recent fMRI study by Krull et al. (2016) demonstrated the potential utility of neuroimaging for identifying markers or potential drivers of neurodevelopmental change following pediatric cancer. In this study, the authors identified negative associations between SEN response (in ACC) during an attention task and prior methotrexate exposure during cancer treatment in ALL survivors (see Fig. 3b). Identification of markers of adverse neurodevelopmental outcomes may help to not only identify individuals who may benefit from intervention, but also lead to new avenues for the development of neuro-protective techniques to be given as an adjuvant during treatment (e.g., folate therapy and adjunctive pyridoxine and cobalamin supplementation).

The fMRI studies by Conklin et al. (2015) and Zou et al. (2012, 2016) coupled fMRI with a cognitive training intervention in cancer patients/survivors, to identify neural mechanisms underlying therapeutic change. For instance, Conklin et al. (2015) examined the short-term efficacy of a 25-session internet-based cognitive computerized intervention (Cogmed, www.cogmed.com) and neural correlates of cognitive changes in children who received CNS-directed therapy for ALL or brain tumor (ages 8–16 years). Survivors were randomly assigned to intervention or waitlist, and fMRI was used to examine neural responses during a spatial working memory task at pre- and post-intervention time points. They found that, relative to waitlist controls, survivors completing the intervention demonstrated greater improvements in working memory, attention, and processing speed. In a follow-up study, these cognitive benefits were even maintained six months later (Conklin et al. 2016). FMRI scanning revealed that improvements in behavioral performance were accompanied by a significant pre- to post-intervention reduction in activation of frontal regions that are considered part of the SEN (i.e., ACC) and CEN (i.e., lateral PFC), during a spatial working memory task (see Fig. 4, top and lower left). These results suggest greater neural efficiency in brain areas known to support working memory, following a computerized cognitive training intervention. In addition, lower pre-intervention responses in dorsolateral PFC, a region of the CEN, were predictive of positive intervention response (Fig. 4, lower right; Conklin et al. 2016). These exciting results suggest that changes in CEN and SEN functioning may represent the neural bases of training-based behavioral change. They also demonstrate the potential utility of baseline neuroimaging for predicting intervention response, and guiding the selection of personalized interventions.

Only one published fMRI study has evaluated rsFC in young cancer survivors (15 ALL survivors [ages 8–15] relative to 14 matched controls; Kesler et al. 2014). In this study, rsFC

between several brain regions was altered, including reduced rsFC of hippocampus and amygdala (part of the SEN) with several regions involved in attention and visual processing (e.g., occipital areas) in survivors relative to controls (see Figs. 5 and 6). Although no group differences in cognitive functioning were observed between survivors and controls, lower amygdalar and hippocampal rsFC was associated with poorer cognitive functioning (i.e., IQ, Color Naming; Kesler et al. 2014). This study was the first to identify disruptions in intrinsic brain connectivity in pediatric cancer survivors, and suggests that alterations in rsFC may be detected even when objective cognitive functioning seems normal. Similar to other neuroimaging studies in survivors (e.g., Kesler et al. 2016), time since treatment and treatment intensity were not related to rsFC. These findings suggest that neuroimaging correlates of pediatric cancer can be observed as early as six months off treatment, and may reflect disruptions in more global patterns of brain organization following a developmental insult (i.e., CNS-directed cancer treatment or childhood adversity). In addition, lower rsFC was related to younger age at diagnosis in the ALL group, suggesting that younger children are more vulnerable to neurobiological changes, and therefore adverse cognitive, behavioral, and emotional consequences, following cancer. This is consistent with observations from behavioral and psychological research, for e.g., higher treatment intensity, younger age at diagnosis, and female gender are associated with poorer emotional health (e.g., higher PTSS; Bruce 2006) and poorer performance on a range of neuropsychological tasks (e.g., sustained attention, visuo-motor control; Smibert et al. 1996; Buizer et al. 2005a; Buizer et al. 2005b).

Neuroimaging studies in adult survivors of childhood cancer

An analogous literature search identified 16 studies of brain structure or brain function in adult (i.e., ages 18) survivors of childhood cancer (Table 2). Most studies used structural MRI or DTI to measure brain structure, and only three studies (19%) used fMRI to examine task-based neural activity ($n = 2$) or rsFC ($n = 1$). Just over half (56%) of the identified studies included ALL survivors, 37% included CNS tumors, and one study (6%) examined Hodgkin Lymphoma survivors. The majority (81%) of the 16 studies linked structural or functional neural variation to measures of cognitive or behavioral functioning (e.g., working memory). None linked neural variation to physical (e.g., ataxia), emotional (e.g., anxiety), or quality of life outcome measures.

Structural or diffusion MRI studies

Similar to structural neuroimaging studies in children, neuroimaging studies in adult survivors of childhood cancer commonly report reductions in volume or indicators of white matter macrostructure, including frontal, parietal, and temporal areas implicated in memory, affect, and executive functioning (see Fig. 7a; King et al. 2015a; Brinkman et al. 2012; Schuitema et al. 2013; Dellani et al. 2008; Porto et al. 2008). Of note, one study reported no difference in white matter macrostructure among adult survivors of pediatric ALL treated with chemotherapy only and matched controls (Genschaft et al. 2013), while another study reported regional *increases* in indicators of white matter macrostructure within several pathways (e.g., uncinate fasciculus, cingulum bundle) in adult survivors of childhood ALL, regardless of treatment (chemotherapy, radiation), which also corresponded with poorer

neurocognitive functioning (e.g., memory span; Edelmann et al. 2014). Edelmann et al. (2014) speculated that *increased* white matter macrostructure among survivors may reflect glial scarring or white matter compaction. Also in agreement with studies in children, white matter alterations are observed irrespective of location of the tumor and treatment, although white matter alterations appear to be exacerbated among adults who received cranial radiation therapy relative to chemotherapy alone as children. Younger age at treatment is related to worse neuroanatomical outcomes among adult survivors (see Table 2). Taken together, these findings indicate persistent disruptions in white matter development among adult survivors of childhood cancer.

Five studies reported reduced volume or shape alterations of the hippocampus among adult survivors of pediatric ALL (Monje et al. 2013; see Fig. 7b; Edelmann et al. 2014; Zeller et al. 2013; Armstrong et al. 2013) or brain tumor (Nagel et al. 2004; see Table 2; Jayakar et al. 2015). Several studies linked hippocampal atrophy to poorer neurocognitive functioning (e.g., episodic memory; see Table 2). In addition to the hippocampus, reductions in caudate, putamen, and SEN regions (amygdala, thalamus) are reported among adult survivors of ALL and brain tumor (Jayakar et al. 2015; Zeller et al. 2013; Porto et al. 2008). Reductions in these areas were also reported in young survivors of childhood cancer (see Table 1), indicating persistent disruptions in subcortical development.

Functional MRI studies

Four studies used fMRI to examine neural correlates of pediatric cancer in adult survivors. In addition to hippocampal atrophy, Monje et al. (2013) report altered hippocampal activation during memory encoding in 10 adult survivors of childhood ALL relative to 10 matched controls (see Fig. 7a). Whereas controls recruited hippocampus during the encoding of items that were later remembered, ALL survivors showed the reverse—they recruited the hippocampus during the encoding of items that were later forgotten, which the authors interpreted as reflecting ineffective neural recruitment following pediatric cancer (Monje et al. 2013). Neurobehavioral responses to working memory have also been examined among adult survivors of childhood cancer. Consistent with studies in youth, adult survivors of childhood cancer (i.e., brain tumor) demonstrate increased neural response in fronto-parietal areas during higher load (i.e., 2-back) conditions, relative to controls (King et al. 2015a; see Fig. 7b). Similarly, performance was worse for higher load (i.e., 2- and 3-back) but not lower load conditions (i.e., 0- and 1-back) in survivors relative to controls, and higher BOLD response in frontal regions was associated with poorer working memory performance during the 2-back condition. Taken together, these findings suggest that adult survivors of childhood cancer engage greater neural resources in response to increased demands of working memory relative to controls. The pattern of increased neural response and poorer performance for higher- but not lower-demanding conditions is consistent with an *ineffective* compensatory neural mechanism that has been observed in working memory studies of *young* brain tumor survivors (e.g., Robinson et al. 2014). In other words, survivors display a ramping up of cognitive and neural resources in the context of poorer behavioral performance to more demanding memory conditions (King et al. 2015a), and that this neurobehavioral dysfunction persists well into adulthood.

To date, only one study has examined rsFC among adult survivors of pediatric cancer. Chen et al. (2016) observed increased rsFC in frontal regions of the CEN, SEN, and DMN (see Fig. 7c). Consistent with the notion of (ineffective) compensatory neural functioning, the authors speculated that increased rsFC among frontal regions may reflect a need for a higher level of cognitive effort among survivors that requires recruitment of additional higher-order brain regions (Chen et al. 2016). Although we identified only two studies that examined functional regional interactions in child, adolescent, or adult survivors (Chen et al. 2016; Kesler et al. 2014), these studies are important because they suggest that well-documented regional changes (for e.g., in hippocampus) are accompanied by changes in neural organization at the network or whole-brain level. Examining neural network dynamics may provide better mechanistic understanding of cognitive or affective disruptions following pediatric cancer, as brain regions do not operate in isolation, and cognitive and affective processes rely on interactions between a distributed set of brain regions and networks.

Summary and gaps in current literature

In summary, our literature review identified 65 neuroimaging studies in child or adolescent patients or survivors, and 16 in adult survivors of childhood cancer. Together, most studies (83%) used structural MRI or DTI to examine brain structure (e.g., volume, thickness, or integrity of gray or white matter). Fewer studies used fMRI, with 14 task-related fMRI studies, and two rsFC studies. Studies in adults are critical because they demonstrate that neurological consequences of pediatric cancer are lasting, and can be detected years and even decades following the conclusion of treatment. Evidence of persistent neurobiological changes following pediatric cancer underscores the potency of this developmental experience, and motivates early prevention and intervention efforts that are capable of moving individuals off a harmful neurodevelopmental trajectory and on to a healthier one. Intervening early during brain development capitalizes on the inherent plasticity of the developing brain that may allow for more enduring positive effects. We assert that research in childhood, proximal to the time of brain injury and insult, will be essential for identifying (1) age-appropriate targets for such interventions, and (2) developmental periods of sensitivity to insult and intervention.

We identify at least two major gaps in our current understanding. First, while most studies link neural changes with cognitive dysfunction, only five studies linked neural changes with emotion-related psychological outcomes (e.g., internalizing symptoms, emotional adjustment) or quality of life measures (see Table 1). This is surprising, given that psychosocial and emotional difficulties are well documented in survivors of pediatric cancer, and many brain regions found to be consistently altered in survivors (e.g., amygdala, hippocampus, insula, PFC, ACC) also play a pivotal role in emotion processing and regulation (Etkin et al. 2015; Etkin et al. 2011; Phelps & LeDoux 2005). Alterations in these regions are centrally implicated in the development and expression of emotional disorders, including anxiety, depression, and PTSD (see meta-analyses by Etkin & Wager 2007; Hamilton et al. 2012). To our knowledge, no neuroimaging studies to date have used task-based fMRI to evaluate neurobehavioral processes associated with active emotion processing or regulation in pediatric cancer survivors.

Second, observed neurobiological changes are largely attributed to neurotoxic effects of cancer treatments on brain development – with several studies demonstrating dose-dependent effects of cancer treatment intensity (i.e., dosage, modality) on brain structure and function (e.g., Qiu et al. 2006; Reddick et al. 2005a, b; see Tables 1 and 2). The role of childhood adversity, in the form of threat exposure, in pediatric cancer has been largely ignored in the existing neuroscientific literature, despite the presence of significant threat to life and physical integrity associated with the disease and its invasive medical procedures. The disconnect, both regarding the measurement of emotion-related psychological outcomes in studies of neural development and the potential drivers of change (i.e., threat exposure, cancer treatment), constitutes a critical barrier to identifying pathways through which childhood cancer impacts neural development, and ultimately, psychological wellbeing. The field lacks a neurodevelopmental framework that considers the joint effects of early threat and cancer treatments, and could provide a more integrative understanding of cancer-related changes across cognitive, behavioral, and emotional domains.

An integrated neurodevelopmental framework

To address this gap in the literature, we propose a novel neurodevelopmental framework that considers childhood cancer as a type of childhood adversity, specifically an *early threat exposure*, and considers the joint impact of early threat and cancer treatments on specific sensitive brain systems (see Fig. 1). We argue that this framework may be helpful for identifying pathways through which childhood cancer impacts neural development, and ultimately, cognitive, behavioral, and emotional sequelae. We build the framework of childhood cancer as a type of early threat exposure based on the existing literature on neurodevelopmental consequences of other more commonly-studied threat-related childhood adversities (e.g., violence, abuse) and integrate these neurodevelopmental consequences with research on psychosocial and neurocognitive consequences of childhood cancer.

Childhood cancer as a form of early threat exposure

Existing neuroscientific research on childhood adversity indicates that different types of exposures have distinct effects on brain development. A recent neurobiological framework proposed by McLaughlin et al. (2014) differentiates between *deprivation* (e.g., neglect) and *threat* (e.g., community/domestic violence, physical/sexual abuse, assault) as core dimensions of childhood adversity that have strong and distinct effects on neural development. Although experiences of violence and abuse differ in many ways from childhood cancer (e.g., context, nature), we assert that these experiences share a common element of early threat that is thought to lead to certain neurodevelopmental adaptations in violence and abuse, and may also contribute to similar neurodevelopmental changes following pediatric cancer.

The ‘active ingredient’ in threat exposure is the presence of unexpected inputs that represent significant threats to the physical integrity or wellbeing of the child (McLaughlin et al. 2014). This is largely consistent with the cancer experience. Childhood cancer involves the presence of a life-threatening disease that evokes a great sense of uncertainty about the future that remains throughout the lifespan. At the same time, families are confronted with

an unpredictable and uncontrollable course of cancer treatment, including intrusive, unfamiliar, and sometimes painful medical procedures that may leave the patient and caregivers to feel immense helplessness. Together, these distressing experiences contribute to high rates of PTSS among patients and their family members, which may take the form of intrusive thoughts, avoidant behaviors, hyperarousal, dissociation, and negative changes in mood or cognition (American Psychiatric Association 2013). As many as 75% of young adult survivors of childhood cancer report re-experiencing traumatic parts of cancer, and nearly 50% report increased physiological responses when reminded of cancer (Rourke & Kazak 2005; Price et al., 2016b). Given these data, PTSS has emerged as one of the most important psychological consequences of childhood cancer (Kazak et al. 2001; Erickson & Steiner 2001). Consistent with our conceptualization of childhood cancer as a form of threat exposure, PTSS is more commonly linked to experiences of life threat rather than deprivation (e.g., neglect) (Sullivan et al. 2006). This is also reflected by diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as the ‘trauma’ must involve exposure to actual or threatened serious injury, violence, or death (American Psychiatric Association 2013; see Kangas 2013 for discussion of diagnostic criteria in the context of cancer).

Of note, although we propose that the early threat exposure dimension is a useful starting point for understanding the effects of childhood cancer on neural development, there are many important differences between childhood cancer and other more commonly-studied forms of early (i.e., physical/sexual abuse, assault, domestic violence, community violence). That is, while these experiences share an element of early threat, they are not the same in other important ways (e.g., family functioning, chaotic environment). For instance, violence and abuse can be systemic, encompass the whole of a child’s ecological environment, and is often perpetrated by a family member or another trusted individual. Childhood cancer, in contrast, can be very specific and focal, and does not necessarily pose a threat to the primary attachment relationships. However, cancer may have the additional burden of chronic impairments and physical disability, which can also represent early adversity for some children. These factors will be considered in more detail, below.

Sensitivity of the hippocampus and regions of the salience and emotion network (SEN) to pediatric cancer and its treatment

Changes in the brain are a proximal indicator of the biological embedding of cancer-related change during development, and should reveal mechanisms by which individual differences or environmental factors modulate cognitive, behavioral, and emotional outcomes (see Fig. 1). Due to the heterochronous nature of brain development, certain brain areas may be particularly vulnerable to developmental insults related to threat exposure or CNS-directed cancer treatments during periods of brain development such as during childhood. Brain areas that play a central role in threat-related processing, learning, or memory are also likely to be altered in response to significant threat to life or physical integrity. The model proposed here considers the vulnerability of the hippocampus and regions of the “salience and emotion network” (SEN) to developmental insult, and aims to link the diverse functions of these brain systems (e.g., memory, attention, emotion processing and regulation, cognitive control)

to the array of cognitive, behavioral, and emotional disruptions observed among patients and survivors of childhood cancer. Sensitivity of the hippocampus and SEN to pediatric cancer is supported by our literature review. We found several studies that reported structural and functional changes in the hippocampus and various SEN regions in childhood cancer patients and survivors, including amygdala, thalamus, nucleus accumbens, insula, and ACC (see Tables 1 and 2, Figs. 2, 3, 4 and 5). Although we assert that the hippocampus and regions of the SEN are likely vulnerable to developmental insults, we are not arguing that these are the only brain systems affected. Altered development of those areas and their connections may lead to disrupted integration into larger-scale brain systems, or compensatory effects in other brain areas or systems (e.g., PFC). These processes likely evolve over time and over the course of brain development.

The SEN is involved in a wide range of cognitive and affective functions by detecting and orienting attention to biologically or cognitively relevant internal and external stimuli (Seeley et al., 2007), and is thus critical to understanding cancer as a threat exposure. The SEN is anchored in the insula and ACC, but also encompasses several subcortical regions that allow for integration of salient affective and motivationally-relevant cues into processing. Subcortical areas include: the amygdala—involved in emotional learning and expression; the thalamus—involved in emotional attention and awareness; the ventral striatum (including nucleus accumbens)—involved in reward evaluation and incentive-based learning; and the substantia nigra/ventral tegmental area (VTA)—a midbrain region home to dopamine cells that signal motivational value or salience (e.g., rewards or threats) and prime the rapid detection of potentially significant cues (Seeley et al., 2007; Berridge 2007; Smith et al. 2011; Pessoa & Adolphs 2010). Given its position at the interface of cognitive, homeostatic, motivational, and affective systems of the brain, the SEN is well positioned to adaptively guide behavior. Although the SEN plays a central role in socioemotional processing, it contributes to a variety of complex brain functions through the integration of sensory, emotional, and cognitive information. Once a salient event has been detected, the SEN facilitates access to attention and working memory resources. This distinctive role underscores the potential for profound disruptions in cognitive and affective functioning should development of the SEN be altered (see review by Menon 2011).

Separate lines of evidence converge on the hippocampus as a brain area that is sensitive to neurotoxic effects of chemo- and radiation-therapy, but also neurotoxic effects of threat exposures during sensitive periods of brain development (Heim & Binder 2012). Broadly, the hippocampus is involved in spatial navigation within an environment and forming long-term memories for events that occur within an environment (see review by Buzsáki and Moser 2013). Although the hippocampus is typically not considered to be part of the SEN, it is densely interconnected with various SEN regions, including amygdala, ACC, insula, VTA, and ventral striatum (Witter 2010), and participates in emotional processing, and the transfer of salient events (including emotional events) into long-term memory. Thus, salient emotional events, such as those associated with significant threat to life or physical integrity, are likely to be strongly held in memory, and may thus alter functional and structural development of the hippocampus. Another factor that may contribute to the sensitivity of the hippocampus to pediatric cancer is that it is one of few brain areas that shows active postnatal neurogenesis (Kohman & Rhodes 2013), which may render it more sensitive to

developmental insults. Indeed, animal models demonstrate adversity-related suppression in hippocampal neurogenesis, and remodeling of dendritic and spine morphology (Joëls et al. 2007). Likewise, radiation and cytostatic drugs are shown to induce long-lasting and progressive neurotoxic effects by damaging neural progenitor cell populations (Monje & Dietrich 2012; Dietrich et al. 2015). The contribution of each of these mechanistic processes to changes in neural development, and ultimately, cognitive, behavioral, and emotional outcomes in children is unknown.

Importantly, many neurodevelopmental changes observed in patients and survivors of childhood cancer are similar to those reported in individuals exposed to other forms of threat, including violence and abuse (see Fig. 8). For instance, individuals exposed to early threat demonstrate reduced hippocampal volume (Fig. 8a; for a meta-analysis see, Riem et al. 2015); reductions in frontal and temporal white matter volume or macrostructure (e.g., uncinate fasciculus FA; Hanson et al. 2015; Huang et al. 2012); impairments in working and episodic memory (see Pechtel & Pizzagalli 2011 for a review); increased compensatory SEN response during an executive control task (Fig. 8b); altered amygdala rsFC with temporo-occipital regions (Fig. 8c); altered SEN rsFC and task-related activation (Fig. 8d); and variation in whole brain structural organization (Fig. 8e). The convergence of findings from neurobehavioral studies in pediatric cancer survivors and individuals exposed to interpersonal threat during childhood raises the notion that certain brain areas, particularly hippocampus and SEN regions, are vulnerable to different types of developmental insults in early life (i.e., neural adaptations following early threat or neurotoxicity related to CNS-directed cancer treatments). Examining the potential commonalities and differences among these childhood threat exposures may provide new understanding of neurodevelopmental consequences of childhood adversity, and neurobiological substrates of adversity-related cognitive and affective impairments that are frequently observed in the wake of both pediatric cancer and interpersonal threat exposure.

It is also important to consider potential areas of divergence, and salient areas of intact functioning between pediatric cancer survivors and individuals exposed to more commonly-studied forms of early threat (e.g., domestic violence, physical and sexual abuse). For example, white matter lesions are commonly reported in the context of pediatric cancer and other forms of brain injury (e.g., traumatic brain injury), but not in studies of interpersonal threat exposure during childhood. In addition, while processing speed, attention, and memory appear to be impaired in both populations, auditory-linguistic domains (e.g., vocabulary, language comprehension) may be relatively spared (Kavanaugh et al. 2017; Riccio et al. 2010). Evaluating the areas of divergence and common areas of intact functioning may provide clues about the role of these environmental experiences in shaping development of specific neural systems.

Given the broad and integral role of the hippocampus and SEN in an array of cognitive and affective processes, evaluation of hippocampal and SEN development may provide a more integrative framework for understanding cognitive, behavioral, and emotional consequences of pediatric cancer. A more integrative network-oriented framework may help to link the existing studies reporting disruptions in localized brain areas (e.g., ACC) or processes (e.g., working memory) with initial reports of altered interactions within and between large-scale

neural networks (e.g., DMN-SEN). For instance, we have previously shown disruptions in localized SEN regions (e.g., insula) in youth exposed to interpersonal threat (e.g., violence, abuse) that relate to altered neurocognitive functioning (e.g., conflict interference) and connectivity within the SEN, and between SEN and DMN (Marusak et al. 2015a). Given that the SEN undergoes dramatic reorganization throughout childhood that span both within- and across-network links (Marusak et al., 2017a, b; Uddin et al. 2011), evaluating how pediatric cancer affects the construction and developmental trajectories of the SEN and other neurocognitive “core” networks (i.e., CEN, DMN) may provide unique insights into neurodevelopmental consequences.

Emotional learning and memory

Together with the hippocampus, the SEN plays a key role in emotional learning and memory, and particularly relevant in the context of threat exposures such as pediatric cancer—threat-related learning. Central in this system is the amygdala, which detects whether a stimulus, person, or event is threatening (LeDoux 2003). The role of the hippocampus is to encode contextual features surrounding the aversive stimulus or threatening event, and to regulate the expression or suppression of fear across different contexts (see review by Maren et al. 2013). Emerging research demonstrates that exposure to threatening circumstances early in life can alter fear learning and memory and the underlying neural structures. In one recent study (McLaughlin et al. 2016), a group of children and adolescents exposed to interpersonal threat (physical abuse, sexual abuse, or domestic violence), ages 6–18, and a matched group of unexposed youth underwent a cued fear conditioning paradigm during which blue or yellow cartoon bells (conditioned stimulus, CS) were paired or unpaired with a startling alarm noise (unconditioned stimulus, US). Threat-exposed youth demonstrated blunted physiologic (skin conductance) responses to the threatening cue (i.e., CS+) and showed a lower ability to discriminate between threat (CS+) and safety (CS-) cues. Lower physiologic response to the threatening cue was associated with lower volume of the amygdala and hippocampus among threat-exposed youth. These findings are important because they demonstrate that exposure to threat in early life may fundamentally change neurobehavioral mechanisms of emotional learning, which may lead to disrupted maturation of the SEN and interconnected systems, and aberrant social, affective, and cognitive development. Neurobehavioral mechanisms underlying threat, emotional learning, and memory have yet to be tested in childhood cancer survivors, and may contribute to problems associated with emotional learning among childhood cancer patients and survivors, including PTSS, treatment-related phobia, social anxiety, and school avoidance (e.g., Bessell 2001; Kazak et al. 2001).

Distorted perception of threat and safety may alter a child’s ability to learn and interact with others in social circumstances. Thus, evaluation of emotional learning mechanisms may shed new light onto social difficulties observed in many pediatric cancer survivors, including diminished social competence (e.g., Schulte & Barrera 2010), poor social skills, and difficulties with peer relationships (e.g., Mahajan & Jenney 2004). These difficulties are likely compounded by chronic impairment and physical disability, and feeling like they are different from other children, which can lead to loneliness, social isolation, exacerbation of internalizing problems, and poor academic achievement due to both neural and

psychological consequences. The ability to interpret, regulate, and respond appropriately to social cues relies on the hippocampus and the SEN. It is not surprising, then, that these areas are centrally implicated in the pathophysiology of anxiety and depressive disorders, which show a sharp increase in incidence during the transition into adolescence (Kessler et al. 2005). This increase further motivates interventions that target hippocampus, SEN, and emotional learning mechanisms as a means of improving social and emotional adjustment among survivors.

Another neural mechanism for emotional learning depends on the connections between the hippocampus and the VTA, which are considered critical for the gating of novel or salient information into long-term memory (Lisman & Grace 2005). We have recently shown reduced rsFC in hippocampal-VTA circuitry in children and adolescents exposed to interpersonal threat relative to unexposed youth (Marusak et al., 2017b). Lower connectivity in this circuitry suggests a novel mechanism that may serve to adaptively prevent the overwriting of a previously stored trauma memory, but at the same time contribute to the broad range of cognitive, behavioral, and emotional difficulties linked to early threat exposure. It is possible that this circuitry is also altered in pediatric cancer patients and survivors.

Together with the hippocampus, SEN regions are key targets of the mesocorticolimbic dopamine pathway, involved in reward and motivation processing. Deficits in reward processing and motivation are clinical and neurobiological hallmarks of depressive disorders (see meta-analysis by Zhang et al. 2013; see Bogdan et al. 2013). Stress-related alterations within the mesocorticolimbic pathway, particularly while the system is still developing, may contribute to the development of affective disorders. In line with this hypothesis, we and others have found deficits in brain and behavioral measures of reward sensitivity among youths exposed to interpersonal violence (e.g., Marusak et al. 2015b; Marusak et al. 2015a; Guyer et al. 2006) and youth at elevated risk for the development of depressive disorders (e.g., Norman et al. 2012). Thus, reward and motivation neurobehavioral processes represent an open area of inquiry for understanding mechanisms underlying affective dysfunction in childhood cancer survivors.

The role of the SEN in cancer-related pain and cognitive dysfunction

The SEN is involved in a diversity of homeostatic functions beyond socioemotional processing. Of relevance in the context of pediatric cancer is pain expectation, perception, and distress. Pain related to medical procedures, treatment side effects, or the cancer itself is a major source of compromised quality of life among children with cancer and their families (Zebrack & Chesler 2002). Recent longitudinal studies indicate that the burden of cancer-related pain does not end when treatment concludes: many survivors of childhood cancer report cancer-related pain well into adulthood (Lu et al. 2011). Given the central role of the SEN in pain perception, altered development of the SEN may represent a neurobiological target for understanding and treating cancer-related pain. Interestingly, neuroimaging work in adults suggests that the SEN is not only involved in first-hand experiencing of pain, but also complex social emotions, including empathetic responses to emotional distress and perceiving pain in others (Singer et al. 2004). Engagement of the SEN to more vicarious

instances of pain and distress may have important implications for adverse cognitive, behavioral, and emotional outcomes in family members, such as parents or siblings, who often witness patients receiving medical treatments and exhibit PTSS in rates that frequently exceed those reported by the patients themselves (e.g., Alderfer et al. 2003).

Another core function of the SEN is controlling engagement of other large-scale neural networks that facilitate access to working memory and attentional resources (e.g., CEN). Thus, characterizing development of the SEN following cancer may shed new light into mechanisms underlying cognitive dysfunction. For instance, altered SEN development may contribute to attentional difficulties, which remain extremely prevalent (up to 67%) among ALL survivors following contemporary chemotherapy-only treatment (Conklin et al., 2012a, b; see meta-analysis by Iyer et al. 2015). Evaluation of the SEN may also provide new insights into potential protective mechanisms and interventional approaches, given research showing that attentional control plays an important role in children's immediate and longer-term responses to cancer-related medical procedures (Trentacosta et al. 2016).

To summarize, our integrated neurodevelopmental framework considers childhood cancer as a type of childhood adversity, specifically an *early threat exposure*, and considers the joint impact of threat and cancer treatments on neural development (see Fig. 1). We suggest that changes in the brain may confer alterations in core cognitive and affective processes (e.g., elevated threat processing, decreased attentional control) that increase risk for cognitive, behavioral, and emotional problems in some youth. We also suggest that brain areas that are sensitive to (1) developmental insults during childhood (e.g., ongoing development or active postnatal neurogenesis), or (2) that are centrally involved in threat-related processing, may be critical for identifying pathways through which childhood cancer impacts neural development, and ultimately, psychological outcomes. We offer the hippocampus and the SEN as key brain systems of interest, based on existing neuroimaging studies in pediatric cancer survivors and in children exposed to other forms of early threat (e.g., violence, abuse).

Directions for future research

Consideration of other external and individual difference factors

Although we focus on threat here, given that the threat to life and treatments represent significant dangers to the physical integrity or wellbeing of the child and are also reported to be the most distressing aspects of the experience (Alderfer & Kazak 2006), we acknowledge that there may be other external factors that cause some children to be on a different playing field before ever being diagnosed with cancer. These factors may include exposure to deprivation, other types of threat exposures or unstable home environments, neighborhood quality, race, or socioeconomic status (SES; see Fig. 1; e.g., Aber et al. 1997; Chen & Miller 2013; Hackman & Farah 2009; Lucas et al. 2017; Saban et al. 2014; Stepanikova et al. 2017). These factors may play an important role in moderating neurodevelopmental outcomes. For example, families of a child with cancer and lower SES might have fewer resources to deal with stress or have reduced access to high quality healthcare, thus exacerbating negative outcomes. This notion is supported by empirical data showing that socio demographic risk factors (e.g., single parenting, lower annual family income, caregiver

education level) predict cognitive and behavioral outcomes following childhood cancer (e.g., Bemis et al. 2015; Uphold et al. 2013). In addition, national survey data indicate that over 70% of children will experience at least one type of interpersonal threat (e.g., abuse, bullying, witnessing violence) before age 18, many of which are linked to dysfunctional family life (Finkelhor et al. 2009). Given the known links between interpersonal threat exposures and psychological and neurodevelopmental outcomes, a more comprehensive and diverse approach to measuring environmental exposures should aid our understanding of mechanisms and outcomes following pediatric cancer. Given also that low SES and minority populations are more likely to suffer from adverse cancer-related effects (Meeske et al. 2007; Uphold et al. 2013; Zeltzer et al., 2009b) and are more likely to experience other forms of adversity (e.g., violence, discrimination; Gillespie et al. 2009; Penner et al. 2016; Taylor & Turner 2002; Kessler et al. 2010), research focusing on high sociodemographic risk populations may help to reduce health disparities. For example, our research is centrally located in Detroit, Michigan, a low-resource minority city that is disproportionately burdened by adversity and associated physical and mental health problems. Despite increased risk, minorities are underserved in healthcare and underrepresented in medical research, and therefore more research in minority communities is needed to address these disparities.

An interesting question for future research is how neurodevelopmental consequences of childhood cancer differ from, or are similar to, those related to more commonly-studied forms of early threat (e.g., violence, abuse). There may also be converging areas of intact function in individuals exposed to childhood cancer and those exposed to interpersonal threat. Identifying the potential relational, emotional, and contextual factors that are operating in childhood cancer vs. interpersonal threat may be critical for understanding developmental outcomes. For instance, the source of the threat is conceptually different; in violence and abuse the threat is interpersonal, often involving someone that the child trusted, whereas in cancer it is the disease itself or related medical procedures. These differences may be relevant for how children process and cope with these threats, and the form and quality of family and social support. We have heard firsthand from the families that participate in our studies that these differences matter. One mother had suffered childhood abuse and recently had a child complete treatment for cancer. She relayed that childhood abuse or other types of family violence are often “undercover” and rarely talked about. The child often feels that he/she has no one to turn to for comfort and security - especially if the caregiver is the perpetrator. Attachment research has shown that such safe and protective early relationships are critical for long-term psychological wellbeing (Ainsworth 1979; Sroufe et al. 2005). In contrast to the isolating experience of childhood violence or abuse, childhood cancer is “out in the open” and has been called a “family disease”, as families frequently report feeling closer in the wake of this experience (Duran, 2013a, b). Many individuals, including medical staff and members of the community, often rally support around the child and their family. Further, unlike common interpersonal threat exposures, childhood cancer does not necessarily pose a threat to the primary attachment relationships. Childhood cancer is, however, associated with chronic impairment and physical disability that is not typically associated with violence or abuse, and may too have long-lasting effects.

These factors may influence whether children deploy maladaptive (e.g., rumination, “I have to go through this alone because I have no one to turn to or who cares”) or adaptive (e.g., reappraisal, “I am strong, I survived this”) cognitive coping strategies following stress. In support of this, children with cancer are more likely to evidence a pattern of resilience and positive growth when referring to a cancer event compared to a non-cancer event (Sharp et al. 2016). These discrepancies are thought to arise from differences in family support, and may help to explain individual differences in psychological outcomes. For example, previous work by our group and others has found that parents’ behavior before and during their child’s painful cancer-related medical procedures influences children’s distress levels (e.g., Cline et al. 2006). Taken together, considering how the early cancer experience is similar to and diverges from other forms of early stress, as well as identifying potential converging areas of intact function, may provide clues into factors that mediate outcomes. This will have important implications for how we diagnose, treat, and support families, and for identifying children at highest risk for adverse outcomes and at greatest need of resources.

Emerging evidence suggests that adversity-related changes in the brain may be independent of the presence or absence of psychopathology, suggesting that individuals are sensitive to neural adaption but may not be sensitive to psychological consequences (see reviews by McCrory et al. 2017; Teicher et al. 2016). Therefore, many adversity-related changes in the brain are thought to reflect a latent vulnerability to psychological problems, rather than an expression of those problems (McCrory et al. 2017). Such adversity-related neural changes are important to characterize among childhood cancer survivors, as not all children will experience psychological consequences (e.g., Trentacosta et al. 2016), but - as we saw in the reviewed literature - many will experience neurological consequences. We argue that understanding neurodevelopmental consequences of pediatric cancer is a necessary first step towards understanding the significant variability in responses and outcomes. It follows, then, that factors that correspond with a greater or lesser degree of neurological change may increase or decrease a child’s risk for the development of psychological negative outcomes, respectively. Several existing neuroimaging studies in pediatric cancer patients/survivors have identified several risk factors for greater degree of neurobiological change, including younger age at diagnosis, tumor location, female gender, cranial irradiation, and increased intensity of CNS-directed treatment (see Tables 1 and 2). Many of these risk factors have also been linked to cognitive impairment in cancer survivors, and many neuroimaging studies link observed neurobiological changes to behavioral or cognitive functioning. As we saw above, however, very few studies have linked neurologic measures to changes in emotion-related psychological functioning.

There are several characteristics of the child (i.e., individual differences) that may play an important role in psychological adjustment among young survivors (see Fig. 1). Researchers have found that neuroticism, defensiveness, conscientiousness, and effortful control are attributes relevant for children coping with cancer (Phipps et al. 2006; De Clercq et al. 2004; Harper et al. 2014a). An important question for future research is whether these attributes relate to brain structural or functional variation observed in pediatric cancer patients or survivors. Such research may critically advance existing psychosocial models by providing new mechanistic insights into individual differences in outcomes.

Genes are individual difference factors that also likely account for substantial variability in outcomes following pediatric cancer. Indeed, emerging research has linked specific genetic polymorphisms to cognitive and behavioral outcomes among pediatric cancer survivors (Cole et al. 2015; Krull et al., 2013a, b). These studies suggest a role for genes related to oxidative stress and neuroinflammation in contributing to chemotherapy-associated neurocognitive decline among pediatric cancer survivors (Cole et al. 2015; Krull et al., 2013a, b). However, to our knowledge genetic factors have yet to be explored as they relate to emotional or neurodevelopmental outcomes in this population. “Imaging genetic” studies demonstrate that common genetic polymorphisms (e.g., in genes encoding brain-derived neurotrophic factor [BDNF] or the oxytocin receptor [OXTR]) modulate structure and function of the SEN and other systems of the brain in children without cancer (Marusak et al. 2016), and that they play an important role in modulating cognitive, psychological, and emotional outcomes in individuals exposed to childhood adversity (see review by McCrory et al. 2010). Thus, genetic polymorphisms may be an area of future study.

Although the prevailing view is that childhood adversity is bad for the developing brain, it is important to consider that some of the adversity-related changes in neurobiological or psychological domains may be *adaptive*. Adaptive changes in nervous system organization prepare the child to avoid or deal with future threats. However, changes that are adaptive in the short-term may be maladaptive later in life (e.g., when re-integrating into normal family, school, and social life, or years down the road), which underscores the need for longitudinal research.

Among the possible changes following cancer, most survivors of pediatric cancer report *positive* psychological changes, including posttraumatic growth (PTG; Gianinazzi et al. 2016; Duran, 2013a, b). PTG is the idea that struggling with and overcoming a significant challenge, such as childhood cancer, can lead to greater self-awareness or appreciation for life, more meaningful interpersonal relationships, or increased sense of personal strength (Tedeschi & Calhoun 1995). PTG may directly relate to positive adjustment outcomes and buffer against negative psychological effects and may be related to the dispositional attribute of “ego-resilience”, which reflects the degree to which a person can endure and “bounce back” after a stressful experience (Eisenberg et al. 2000; Harper et al. 2007). As research on aftereffects of stressful experiences has traditionally emphasized negative outcomes, it is not surprising that there has been little research on neural mechanisms underlying PTG. In fact, we are only aware of one study using MRI to examine the neural correlates of PTG. In this study of healthy adults reporting a range of adversities (e.g., interpersonal conflicts, death of family/close friend, academic failure; Fujisawa et al. 2015), PTG was positively associated with rsFC between the superior parietal lobe (a CEN region) and the supramarginal gyrus - a brain region involved in memory and social functioning. A better understanding of the neural basis of PTG may help establish methods for augmenting positive change for the subset of survivors who do not report some form of PTG (Duran, 2013a, b).

Resolving neurodevelopmental effects of early threat exposure vs. cancer treatments

A major challenge in research on neurodevelopmental consequences of childhood cancer is disentangling effects of adversity from cancer treatment-induced neuronal damage (see Fig.

1). These are not mutually exclusive and are difficult to disentangle. These may also have unique relationships with external and individual difference variables, contributing to individual differences in outcomes. To our knowledge, no neuroimaging studies have examined both, highlighting a critical gap in our understanding of mechanisms of neurodevelopmental change. Variation in the brain may provide early clues about underlying etiological causes or potential protective mechanisms. Although more research is needed to understand how to better resolve these, we offer some recommendations here. One approach would be to simultaneously measure cancer drug exposure and adversity, and test how these variables relate to neural and behavioral measures. Although no neuroimaging studies have measured both, several have demonstrated dose-dependent effects of cancer treatment intensity (i.e., dosage or modality) on brain structure and function. However, results are inconsistent. This may be since drug dosage is widely used as a surrogate for drug exposure, which may introduce measurement error and compromise the accuracy of results. Plasma drug exposure and assessment of central (i.e., neural) and peripheral biomarkers may provide better precision in identifying the source of long-term neurodevelopmental and psychological outcomes.

A recent pioneering study by Krull et al. (2016) measured plasma drug exposure (high-dose methotrexate) and subsequent biomarker response (plasma homocysteine), and linked those measures to neurocognitive and brain imaging outcomes in 218 long-term survivors of childhood ALL (mean age = 13.8 years, $SD = 4.8$) treated with chemotherapy only. They found that higher plasma methotrexate and homocysteine levels were associated with poorer scores on various cognitive measures. Neuroimaging data suggested that higher drug and peripheral biomarker concentrations predicted increased neural response in SEN (e.g., ACC) and CEN regions (e.g., dorsolateral PFC) during a task that measures sustained attention and executive functioning (see Fig. 3b). In addition, higher dexamethasone was associated with a thinner cortex in the ACC and increased axial diffusivity in frontal areas, as measured by structural MRI and DTI, respectively. These gray and white matter changes were associated with neurocognitive impairment (Krull et al. 2016). This study is the first to link plasma drug exposure to neural and cognitive changes following childhood cancer, and provides novel mechanistic insight into pathways leading to psychological late effects. Results are also in line with the notion that regions of the SEN are particularly susceptible to cancer-related drug exposure while the brain is still developing.

We advocate that concurrent evaluation of drug exposure *and* threat/stress may help to more fully explain neurodevelopmental changes, and ultimately, cognitive, behavioral, and emotional consequences. While serum drug exposure provides a useful measure for drug exposure, the best approach to measure adversity is less clear. We and others have previously evaluated pediatric cancer patients' distress and perceptions of life threat (or threat of bodily harm), and had multiple, independent raters assess children's distress during cancer-related medical procedures via video-recordings (e.g., Trentacosta et al. 2016; Harper et al. 2014b; Harper et al. 2013). However, McLaughlin et al.' (2014) neurodevelopmental model of childhood adversity emphasizes the *environmental* aspect of stress (i.e., the circumstances) rather than an individual child's perceptions or responses, which are likely influenced by myriad other factors (e.g., family support, available coping strategies). Indeed, there are enormous individual differences in response to environmental circumstances, and two

children experiencing the same event may have vastly different responses. While these different responses are certainly important for moderating outcomes (e.g., anxiety), the environmental experience itself sets a process of neurodevelopmental adaption in motion (McLaughlin, Personal Communication, March 8, 2017). Complicating the resolution of threat and cancer treatments in the study of pediatric cancer is that these are co-occurring; there are no patients experiencing threat without cancer treatments, and vice versa. However, borrowing from the existing literature on childhood adversity, one approach would be to assess frequency and severity of early threat within this group. For example, frequency (e.g., frequency of invasive cancer-related medical procedures, length of treatment, number of days of hospitalization/hospital visits) and severity (e.g., different treatment modalities, emergency hospitalizations, treatment side effects, deaths of other patients, relapse or reoccurrence) of cancer-related adversity could be measured. It is important to note that the literature on childhood adversity is still evolving, and there is not yet a consensus on the definition and measurement of childhood adversity (McLaughlin 2016). We expect that advances in research on childhood adversity will inform research in the area of pediatric cancer.

Broader application of the model

There are few early experiences as consequential as childhood cancer. Childhood cancer has a radical impact on a person's life, redefining priorities, objectives, and perceptions (see Jim & Jacobsen 2008). As we have seen, following early adverse experiences, individuals experience the world with a fundamentally altered nervous system. Changes at the level of structural and functional neurobiology have been linked to increased risk of behavior problems and cognitive dysfunction. Future studies may also identify neurodevelopmental substrates underlying risk of emotion-related problems, including anxiety, depression, and PTSS among survivors, as well as positive changes, such as PTG. Although we focus on pediatric cancer here, the proposed neurodevelopmental model may have broader applications for understanding psychological and neurodevelopmental consequences for the millions of children who are living with other chronic- or life-threatening illnesses (e.g., hemophilia, sickle cell, HIV/AIDS, chronic pain), or who endure other intensive medical interventions (e.g., intensive care, accidents). For example, although there are many points of difference among these experiences (e.g., treatments, characteristics, onset, duration), there may also be some commonalities among experiences (e.g., invasive medical procedures, diagnosis of a life-threatening injury or illness, threat of reoccurrence or long-term complications) that may be associated with a similar range in child responses (e.g., PTSS; Price et al., 2016b; Kazak et al. 2005) and may also, as we argue, have similar effects on neural development.

Conclusions

Today, children are surviving pediatric cancer at unprecedented rates, making it one of modern medicine's true success stories. However, we are increasingly becoming aware of the negative impact that the early cancer experience has on long-term cognitive, behavioral, and emotional functioning. These adverse effects have been largely attributed to the injurious effects of cancer treatments (e.g., chemotherapy, cranial irradiation) on brain

development. We contend that the effects of pediatric cancer as an *early threat experience* are also important to consider when evaluating psychological and neurodevelopmental consequences. The role of childhood adversity in pediatric cancer – namely, the presence of a life-threatening disease and endurance of invasive medical procedures – has been largely ignored in the neuroscientific literature, despite compelling research by our group and others showing that exposure to other forms of childhood adversity (e.g., violence, abuse) strongly imprints on neural development, and that these neurobiological changes alter core cognitive and affective processes that are thought to increase risk for psychological problems. Here, we offer a novel neurodevelopmental framework that characterizes childhood cancer as a type of early threat exposure, and focuses on the sensitivity of the hippocampus and the “salience and emotion network” (SEN) to early threat and treatment-induced brain injury. This model may help to advance interventions and psycho-social models by identifying new pathways through which childhood cancer impacts neural development, and ultimately psychological outcomes.

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Public significance statements

It is estimated that nearly 500,000 survivors of pediatric cancer will be living in the US by the year 2020. A proportion of these survivors will experience cognitive, behavioral, or emotional difficulties that greatly compromise quality of life, disrupt everyday functioning, and may increase morbidity, mortality, and healthcare costs. Here, we review existing neuroimaging studies on brain mechanisms that may underlie cancer-related psychological problems, and provide a new integrative neurodevelopmental framework that considers pediatric cancer as a type of threat-related childhood adversity, and considers the joint impact of early threat and cancer treatments on specific sensitive brain systems.

Fig. 1.

Top: Early threat exposure and cancer treatments are both developmental insults that can alter neural development and contribute to the range of cognitive, behavioral, and emotional late and long-term effects reported in childhood cancer patients and survivors. Bottom: various potential external (e.g., environment) and individual difference factors could modify these effects. While it is largely recognized that late and long-term effects are due, in part, to injurious effects of therapeutic intervention during cancer treatment (e.g., chemotherapy, cranial irradiation) on the developing brain, we assert that the role of *early threat exposure* in pediatric cancer – namely, the diagnosis of a life-threatening disease and endurance of invasive medical procedures – should also be considered. Early threat exposure, a form of childhood adversity, defined as an experience that is likely to require significant psychological or neurobiological adaptation by the average child and that represent a deviation from the expectable environment (McLaughlin 2016), has been shown to strongly imprint on brain development, and is one of the strongest risk factors for virtually all commonly occurring psychological disorders. Research is needed to understand neurodevelopmental consequences of the ‘double hit’ of early threat and therapeutic intervention associated with childhood cancer, and factors that may modify outcomes. Identification of such factors will be essential for guiding early intervention to mitigate these risks

Fig. 2.

Altered brain structure and function in young survivors of pediatric cancer. **a** Reduced hippocampal volume in $n = 27$ ALL survivors (ages 15–22 years; in remission for 6–18 years) treated with chemotherapy-only, relative to $n = 27$ matched controls (Genschaft et al. 2013). **b** Regional increases (warm colors) and decrease (cool colors) in white matter clustered connectivity, as measured using graph theoretical analysis of DTI data in $n = 31$ young ALL survivors (ages 5–19 years, 6–111 months off treatment) relative to $n = 39$ matched controls. Of note, increased nodal clustering was noted in the ALL group in hippocampus and insula, a core SEN region, and decreased clustering in amygdala, considered a part of the SEN (Kesler et al. 2016). Abbreviations: ALL, acute lymphoblastic leukemia; SEN, salience and emotion network; DTI, diffusion tensor imaging. Image for panel B provided courtesy of Dr. Shelli Kesler. All images are adapted with permission

Fig. 3.

Altered brain function in young survivors of pediatric cancer. **a** Significant increases in response in ACC, a core SEN region, in $n = 8$ young ALL survivors ($m = 14.54$ years, $SD = 2.47$; 4–12 years after treatment) relative to matched controls, during a working memory (n-back) paradigm (2-back condition). No significant differences in behavioral performance (i.e., accuracy, reaction time) were observed between groups (Robinson et al. 2010). **b** Higher plasma methotrexate exposure during treatment for ALL is associated with lower response in ACC, a core SEN, during an attention task at more than five years ($m = 7.7$, $SD = 1.7$) post-diagnosis ($n = 147$; m age at scan = 13.8 years, $SD = 4.8$; Krull et al. 2016). Abbreviations: ALL, acute lymphoblastic leukemia; ACC, anterior cingulate cortex; SEN, salience and emotion network. All images are adapted with permission

pre- to post intervention reduction in SEN and CEN
response during a working memory task

Conklin et al., 2016

Fig. 4.

Function of the salience and emotion network (SEN) and other large-scale neurocognitive networks represent key targets for psychosocial and behavioral interventions. 30 survivors of ALL or brain tumor who completed a 25-week computerized cognitive training intervention exhibited increased behavioral performance in several cognitive domains (Conklin et al. 2016). This improvement in behavioral performance was accompanied by a pre- to post-intervention reduction in SEN (anterior cingulate cortex, ACC) and CEN (lateral prefrontal cortex, LPFC) activity during a working memory task (top and bottom left panels). Additionally, lower pre-intervention activity in CEN (dorsolateral prefrontal cortex) during a working memory task predicted positive treatment response, i.e., greater positive change in working memory performance (i.e., spatial span backward; bottom right panel). Abbreviations: ALL, acute lymphoblastic leukemia; CEN, central executive network; SEN, salience and emotion network

Kesler et al. 2014

Fig. 5. Altered rsFC in young survivors of pediatric cancer. Regional increases (blue) and decreases (green-yellow) in rsFC in $n = 15$ young ALL (ages 8–15 years, 9–110 months off treatment) and $n = 14$ matched controls. In particular, ALL survivors showed reduced rsFC of amygdala ('RAMG') and hippocampus ('LHIP', 'RHIP') with attention and visual regions (e.g., occipital; Kesler et al. 2014). Abbreviations: ALL, acute lymphoblastic leukemia; rsFC, resting-state functional connectivity. All images are adapted with permission

Fig. 6.

Altered brain structure in adult survivors of pediatric cancer. **a** Relative to matched controls ($n = 27$), adult survivors of childhood brain tumor ($n = 27$, ages 18–32; average of 13.7 years [$SD = 5.37$] since diagnosis) demonstrate reductions in indicators of white matter integrity in frontal and temporal areas. White matter integrity in frontal areas was positively correlated with IQ (King et al. 2015b). **b** Altered hippocampal volume and shape in adult survivors of pediatric ALL treated with CRT ($n = 39$, mean age = 26.7 years [$SD = 3.4$]; average of 23.9 years [$SD = 3.1$] since diagnosis) or CT only ($n = 36$, mean age = 24.9 years [$SD = 3.6$]; average of 15 years [$SD = 1.7$] since diagnosis) relative to controls ($n = 23$, mean age = 23.1 years; Edelmann et al. 2014). Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial radiation therapy; CT, chemotherapy. All images are adapted with permission

Fig. 7.

Altered brain function in adult survivors of pediatric cancer. **a** Abnormal elevation in hippocampal activity during encoding of later forgotten items in $n = 10$ adult survivors of pediatric ALL (average age = 30.8 years; 20–30 years after treatment) relative to $n = 10$ matched controls (“CTL”, Monje et al. 2013). Functional neural changes were accompanied by poorer recognition memory and hippocampal atrophy in the ALL relative to control group. **b** Adult survivors of pediatric brain tumor ($n = 17$, average age = 23.39 [$SD = 4.46$]; 15.5 years ($SD = 7.6$) post diagnosis) exhibited greater activation in dmPFC, a SEN region, during a working memory paradigm (2-back condition) relative to matched controls ($n = 17$). Higher dmPFC activation was associated with poorer performance, suggesting an ineffective compensatory neural mechanism – similar to studies in children (Fig. 3a; King et al. 2015a). **c** Increased rsFC among frontal regions in $n = 16$ adult survivors of childhood cerebellar tumors (ages 17–34 years; average of 14.0 years [$SD = 7.3$] since diagnosis) relative to $n = 16$ matched controls (Chen et al. 2016). Abbreviations: ALL, acute lymphoblastic leukemia; SEN, salience and emotion network; rsFC, resting-state functional connectivity; dmPFC, dorsomedial prefrontal cortex. All images are adapted with permission

Fig. 8.

Common alterations in brain structure and function in individuals exposed to more commonly-studied childhood experiences that involve similar elements of early threat (e.g., interpersonal violence, abuse), suggesting a role for neurotoxic effects of early threat exposure in neurodevelopmental consequences of pediatric cancer. **a** Age-related decreases in hippocampal volume of 27 threat-exposed youth with PTSD (mean age = 14.2 years, $SD = 2.7$) relative to 27 matched controls (Keding & Herringa 2015). **b** Increased response in ACC, a core SEN, during a behavioral inhibition task (Go/No-Go) in 16 youth with interpersonal trauma-related PTSS (ages 10–16 years) relative to 14 matched controls (Carrion et al. 2008). No group differences in task performance were observed, suggesting a compensatory neural mechanism that is also observed in pediatric cancer survivors (see Fig. 3a). **c** Relative to 21 unexposed matched controls, 21 youth exposed to interpersonal threat (e.g., violence, abuse) demonstrated altered rsFC between superficial ('SF') amygdala and various regions of SEN (e.g., ACC, insula), prefrontal cortex, and temporal and occipital lobes. Similar to a study of young survivors of pediatric ALL (see Fig. 5), threat-exposed youth demonstrate reduced (negative) rsFC between amygdala and temporo-occipital studies, involved in attention and visual processing (Thomason et al. 2015). **d** Relative to 19 matched controls, 14 youth exposed to interpersonal threat ($Mage = 12.61$ years, $SD = 2.11$) demonstrate reduced SEN rsFC within the ACC, and increased response in insula, a core SEN region, during a cognitive control (conflict) task. Higher insula response was associated with poorer task performance (Marusak et al. 2015a). **e** Increased network centrality of the insula, a core SEN region, in 145 18–25 year-olds with histories of maltreatment exposure relative to 123 matched controls (Teicher et al. 2014). Increased prominence of the insula within a whole-brain network is similar to a report in young ALL survivors (Kesler et al. 2014; see Fig. 5). Network centrality was measured using graph theoretical analysis of structural MRI data. Abbreviations: ALL, acute lymphoblastic leukemia; ACC, anterior

cingulate cortex; SEN, salience and emotion network; rsFC, resting-state functional connectivity; PTSS, posttraumatic stress symptoms. All images are adapted with permission

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Table 1

ies in child and adolescent cancer survivors

Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
The Journal of Pediatrics	103	39	64	Brain tumor (n = 21 MB, n = 18 PA).	MB: 14.7 [6.9–20.4], PA: 12.2 [5.0–18.3]	MB: 6.6 [1.2–15.7], PA: 7.7 [1.4–16.2]	MB: 7.0 [0.3–15.0], PA: 3.4 [1.0–8.6]
Journal of Pediatric Oncology Nursing	17	8	9	Brain tumor	8.5 (1.3) [5–13]	2.65 (1.38) [1.17–4.58]	5.4 (2.9) [2.5–11.4]
The Lancet Haematology	190	190	—	ALL	10–18	4.9 [2–10]	7.35 [6–9]
Brain Connectivity	70	31	39	ALL	11 (3.4)	5.4 (3.7) [2–14]	2.92 (2.58) [0.5–9.25]
Journal of Clinical Oncology	218	218	—	ALL	13.8 (4.8)	6.6 (4.5)	7.7 (1.7)
Neuroimage Clinical	47	47	—	Cerebellar tumor	9.7 (4.8)	>2	[0–1]
Journal of Neuro-Oncology	39	19	20	Brain tumor: PA (n = 10), and MB (n = 9)	12.9 (5.1), [6.5–25.4]	9.3 (4.5)	3.6 (2.1)
Neuropsychology	96	59 (n = 29 surgery with or without focal radiation, n = 30 cranial-spinal radiation)	37	Brain tumor (posterior fossa; n = 17 astrocytoma, n = 8 ependymoma, n = 31 MB n = 1, ganglioglioma, n = 1 germinoma, n = 1 choroid plexus papilloma)	Surgery group: 11.2 (3.6), CSR group: 11.6 (3.5)	Surgery group: 7.1 (3.9) [0.2–15.6], CSR group: 8.1 (2.8) [4.3–15.2]	Surgery group: 4.1 (3.0) [0.3–10.5], CSR group: 3.4 (3.4) [0.0–11.4]
Brain Imaging and Behavior	61	40	21	MB	n = 19 reading--intervention: 11.7 (0.6) and n = 21 standard-of-care: 12.1 (0.6)	reading-intervention: 10 (0.6), standard-of-care: 9.5 (0.6)	Time since tumor treatment, 2.5 [1.2–5.4] and since reading intervention, 2.9 [1.6–5.9]
Journal of Clinical Oncology	68	68 (n = 34 intervention group, n = 34 wait-list controls)	—	ALL (n = 47), brain tumor (n = 21; 4 ependymoma, n = 2 glioma, n = 15 MB/PNET)	Intervention: 12.21 (2.47), Control: 11.82 (2.42)	Intervention: 5.15 (2.92), Control: 4.62 (2.68)	Intervention: 4.97 (3.02), Control: 5.04 (2.41)
Child's Nervous System	34	34	—	Cerebellar tumor (n = 17 pilocytic astrocytoma and n = 17 MB)	MB patients: 13.2 [7.8–20.6], PA patients: 13.1 [9.2–17.5]	MB patients: 7.6 [2.2–16.6], PA patients: 6.7 [0.9–12.2]	MB patients: 5.6 (3.2), PA patients: 6.3 (2.6)
Neuro-oncology	64	32	32	LGG (subtentorial n = 19,	13.99 (3.03) [8.42–19.12]	subtentorial: 7.22 (3.12) [1.60–12.33],	subtentorial: 5.58 (3.95) [0.59–13.26],

Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
Child Neuropsychology	32	17	15	supratentorial n = 13) Brain tumor (n = 9) pilocytic astrocytoma, n = 4 posterior fossa medulloblastoma, n = 3 dysembryoplastic neuroepithelial tumor, and n = 1 craniopharyngioma)	12.60 (2.48) [8–16]	supratentorial: 3.86 (2.26) [1.05–8.41] 6.94 (2.41) [2.06–11.62]	supratentorial: 11.89 (2.52) [8.82–16.76] 5.29 (2.83) [2.13–10.92]
Pediatric Blood and Cancer	32	32	—	MB (n = 18), PA (n = 14)	MB: 15.2 (4.9), PA: 12.6 (5.0)	MB: 11.2 (3.7), PA: 9.9 (4.4)	MB: 3.8 (2.5), PA: 2.6 (2.1)
Journal of Clinical Oncology	369	369	—	ALL	[1–18]	Not stated	Not stated
Journal of Pediatric Hematology-Oncology	66	66	—	ALL	Not stated	P9201: 4.1 [1.1–7.5], P9605: 4.9 [2.3–9.8]	P9201: 5.3 [2.6–7.1], P9605: 5.3 [2.7–7.7]
Pediatric Hematology and Oncology	122	62	60	ALL	6–18	CCG protocol: 5.27 (2.38). Modified BFM 90 protocol: 5.6 (3.19). Modified BFM 83 protocol: 6.33 (3.8)	CCG protocol: 2.72 (0.61). Modified BFM 90 protocol: 4.19 (1.44). Modified BFM 83 protocol: 7.96 (1.98)
Child's Nervous System	18	9	9	Brain tumor (n = 8), T-cell ALL (n = 1)	11.8 (3.7) [5.5–18.6]	Not stated	0–27 months post-CRT
Journal of Neuro-Oncology	50	50	—	Brain tumor (n = 22) ependymoma, n = 16 craniopharyngioma, n = 12 LGG)	13.13 (2.88) [8–18]	6.34 (3.43)	5.77 (2.27)
Pediatric Blood and Cancer	29	15	14	ALL	11.5 (2.0) [8.9–15.9]	4.4 (1.8) [1.5–8]	3.65 (2.45) [0.75–9.17]
Journal of the International Neuropsychological Society	33	20	13	Posterior fossa brain tumor (n = 9) MB, n = 1 astrocytoma)	12.4 [7.2–17.2]	7.2 [4.3–12.8]	5.1 [1.1–11.6]
Neuropsychology	32	17	15	Brain tumor: pilocytic astrocytoma (n = 9), posterior fossa MB (n = 4), dysembryoplastic neuroepithelial tumor (n = 3), and	12.60 (2.48) [8–16]	6.94 (2.41) [2.06–11.62]	5.29 (2.83) [2.13–10.92]

Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
Oncology letters	25	25	—	craniopharyngioma (n = 1) ALL	12.9 (3.2) [8.5–20]	6.9 (3.04) [2.5–13]	>5
PloS One	54	27	27	ALL	17.9 (2.4) [14.9–22.8]	5.6 (2.5) [1.1–10.2]	12.4 (3.0) [6.1–18.5]
The Cerebellum	23	12	11	Cerebellar tumor	11.1 [6–17]	Not stated	[0–1]
Pediatric Blood and Cancer	9	9	—	Posterior fossa brain tumor	14.89 (1.9) [11.50–17.25]	5.00 (2.7) [1.33–8.00]	9.88 (3.4) [6.41–15.35]
PloS One	59	28	31	ALL	12.0 (4.6) [5.0–19.8]	Not stated Not s+ OI3tated	4.19 (2.55) [0.5–10.5]
Archives of Clinical Neuropsychology	42	14	28	n = 7 ALL, n = 7 brain tumor (astrocytoma, ependymoma, MB, suprasella germinoma, suprasella craniopharyngioma)	12.02 (0.09) [6–17]	5.91	> 1
Cancer	97	97	—	ALL	10.84 (3.93) [6.02–21]	8.22 (3.93) [3.46–18.45]	2 (years after end of treatment, time of neurocognitive assessment)
Brain Edema XIV	45	45	—	ALL	[4–17]	Not stated	[6–12]
Brain Imaging and Behavior	59	28	31	ALL	12.0 (4.6) [5.0–19.8]	Not stated	4.19 (2.55) [0.5–10.5]
Pediatric Blood and Cancer	15	8	7	ALL	14.07 (2.32)	4.94	6.46
International Journal of Radiation Oncology Biology Physics	34	17	17	ALL (n = 11) and MB (n = 6)	14 (2.5) [8.9–16.9]	5.2 (3.1) [2.0–13.2]	8.4 (3.5) [2.7–13.6]
Neuropsychology	8	8	—	Posterior fossa brain tumor	[3–15]	Not stated	Began at average of 2 months post-surgery, longitudinal follow-up to average of 2 years later
American Journal of Neuroradiology	197	197	—	ALL	[1.0–18.9]	5.3	N/A (active treatment). Average time between

Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
American Journal of Neuroradiology	23	9	14	ALL	15.17 (5.48) [7.75–25.76]	5.17 (2.96) [1.43–9.36]	two MRI scans, 0.325 (0.67)
Behavioural Neurology	24	12	12	Cerebellar PA	12.5 (4.1) [6–19]	Not stated	9.95 (5.13) [3.48–16.96]
Neuroimage	27	13	14	Posterior fossa brain tumor	12.3 (3.1) [7–17]	Not stated	Not stated
International Journal of Radiation Oncology, Biology Physics	44	22	22	MB	12.1 (4.6)	8.1 (4.6)	3.9 (2.9)
Journal of Clinical Oncology	85	30	55	ALL (n = 18), MB (n = 12)	13.1 [6.0–22.1]	ALL w/out RT: 6.68 (6.32); ALL w/ RT: 6.47 (4.35); MB: 8.52 (3.57)	ALL w/out RT: 6.38 (4.29); ALL w/ RT: 8.39 (4.74); MB: 3.25 (2.26)
Neuro-oncology	16	8	8	MB	9.98 (2.90)	7.48 (3.87)	2.5 (0.72)
Neuroimage	4	2 (Patient A female, Patient B male)	2 (males, aged 23 years and 33 years)	MB	Patient A: 10.7, Patient B: 9.4	Patient A: 10.7, Patient B: 9.5	[0–1]
Cancer	145	112	33 siblings	ALL	9.8 (3.1)	4.1 (2.6)	6.0 (3.5)
Magnetic Resonance Imaging	58	58 (Group A decreased NAWM volume n = 39, Group B increased NAWM volume n = 19)	—	MB	Not stated	Group A: 8.26 (0.7) [3.2–20.18]; Group B: 8.50 (0.8) [3.13–17.97]	[0–2]
Brain	36	22	14	Cerebellar tumor	[10–28]	[1–17]	8.2 [≥3]
Neuro-oncology	52	52	26	MB	Not stated	8.3 [3.4–20.0]	2.5 [0.2–7.9]
American Journal of Neuroradiology	45	45	—	ALL	[1.5–18.6]	Low risk: 5.0 (2.7), Standard/high risk: 9.2 (4.8)	Began at week 6 of remission induction and ended at week 120 of continuation treatment
American Journal of Neuroradiology	45	45	—	ALL	[1.5–18.6]	Low risk: 5.0 (2.7), Standard/high risk: 9.2 (4.8)	Began at week 6 of remission induction and ended at week 120 of continuation treatment
Neuroimage	43	16	16 adults (ages 20–35), 11 siblings (ages 8–16)	n = 8 ALL, n = 8 brain tumor (glioma,	13.2 (2.4) [9–17]	6.27	5.4 (2.3) [2–9]

Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
Pediatric Blood and Cancer Neuroimage	20	10	10	astrocytoma, ependymoma, MB	[6–14]	[3–5]	>3
	32	16	16	ALL	11.1 (4.2) [3.2–18.6]	8.8 (4.6) [2.7–17]	3.1 (1.8) [0.8–6.3]
Journal of the International Neuropsychological Society	37	37	—	Brain tumor (n = 17 MB, n = 7 astrocytoma, n = 5 ependymoma, n = 4 PNET, n = 2 germinoma, n = 1 oligodendroglioma, n = 1 craniopharyngioma)	Not stated	6.5 [1.7–14.8]	5.7 [2.6–15.3]
American Journal of Neuroradiology	25	25	—	MB	4–12	8.27	0.31
Radiology	23	23	—	ALL	Not stated	1–14	N/A (active treatment)
American Journal of Neuroradiology	18	9	9	MB	10.8 [3–19]	7.8 [3–14]	3.6 [1–6]
Pediatric Blood and Cancer	19	19	—	ALL	11.3 [4.6–20.1]	6.0 [2.1–14.8]	Immediately after end of treatment (n = 9) or 4–8 years after end of treatment (n = 10)
Cancer	40	40	—	Brain tumor (n = 18 MB n = 8 astrocytoma, n = 6 ependymoma, n = 4 primitive neuroectodermal tumors, n = 2 germinoma, n = 1 oligodendroglioma, n = 1)	12.8 [7.1–18.8]	6.5 [1.7–14.8]	5.7 [2.6–15.3]
American Journal of Neuroradiology	35	35	—	MB	At most recent MRI: 9.61 (3.77)	7.68 (3.25) [3.2–17.2]	At most recent MRI: 1.92 (0.97)
Journal of Clinical Oncology	42	42	—	MB	12.6 (4.2)	8.2 (3.8)	4.0 (2.7)
Brain	19	19	—	Cerebellar tumors (n = 1 MB, n = 7 astrocytoma, n = 1 ependymoma)	[3.67–16.5]	8.17 [3.25–14.83]	0.43 (0.53) [0.08–1.83]

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Pediatric Blood and Cancer	33	33	—	ALL	Not stated	6.2 [2.1–15.0]	N/A (active treatment)
Magnetic Resonance Imaging	26	26	—	MB	Not explicitly stated - each patient had at least 4 MR examinations over at least of 7 months following CSI	7.3 [3.2–17.2]	1.56 [0.75–2.53]
Annals of Neurology	36	36	—	Brain tumor (n = 18 MB, n = 18 low-grade PF tumors)	Not stated	<21	MB: 3.8 (2.6), PF: 2.6(2.1)
Cancer	32	32	—	ALL	13.2 [8–24]	5.3 (3.5)	5.0 (0.4)
Magnetic Resonance Imaging	94	77	17	Brain tumor	5–21	6.9 [3.3–15.6]	5.1 [1.2–10.6]
	Neuroimaging modalities	Type of study	Physical and physiological outcome measures	Cognitive and behavioral outcome measures	Emotional and quality of life measures	Main findings	
ion, CSI, and CT, PA; Surgical	Perfusion MRI (ASL); DWI	Cross-sectional	—	IQ (n = 12 survivors)	—	Young MB survivors had significantly reduced global CBF compared to controls, but PA survivors had normal CBF. Diffusion abnormalities (lower ADC) were apparent in the hippocampus and amygdala of MB survivors and in the amygdala of PA survivors. In n = 12 patients with IQ assessments, increased regional ADC was correlated with higher IQ- where-as CBF was not related to IQ.	
	DTI	Cross-sectional	—	Executive function, memory	Quality of life	Compared to control subjects, brain tumor patients exhibited significantly lower psychosocial and school functioning and overall quality of life. Indices of gray and white matter injury (elevated mean	

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Journal	DTI	Longitudinal	Fine motor dexterity	IQ, executive function, processing speed, attention, memory	—	—	diffusivity and decreased FA) were apparent in memory and executive functioning areas in patients. Particularly, low inhibition scores correlated with heightened mean diffusivity in prefrontal areas in patients.
							Childhood ALL survivors had more problems with working memory, organization, initiation, and planning in addition to reduced memory span, processing speed, and executive function compared to population norms. Compared to ALL survivors with no history of leukoencephalopathy, ALL survivors with a history of leukoencephalopathy had more problems with organization and initiation, and showed decreased white matter integrity in the frontostriatal tract at long-term follow-up (at least 5 years post-diagnosis).
Journal	DTI	Cross-sectional	—	Coding/processing speed, vocabulary, working memory, perceptual reasoning, visual and verbal learning	—	—	Altered white matter connectome properties (lower small-worldness and network clustering coefficient) and greater cognitive impairment was found in the ALL group compared to controls. Atypical clustered connectivity was apparent in parietal, frontal, hippocampal, amygdalar, thalamic, and occipital regions in

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							the ALL group. Decreased connectivity within neighboring brain regions in young survivors of ALL may be related to reductions in local information processing efficiency.
	Task-based fMRI (executive function "attention network task"), structural MRI, DTI	Longitudinal	Fine motor dexterity	IQ, executive function (cognitive flexibility, verbal fluency, working memory, organization, problem solving abilities), processing speed, attention, memory	—		Though measures of executive function, processing speed, and memory were decreased in ALL survivors relative to population norms, intelligence was unimpaired. Increased plasma concentration of methotrexate was related to decreased executive function. Higher plasma concentration of methotrexate and greater neurocognitive impairment was associated with increased fMRI activation during an attentional task, increased cortical thickness in dorsolateral prefrontal brain regions, and with alterations in frontostriatal white matter microstructure.
	DTI (MRI scans at pre-op, post-op, and 1 year post-op)	Longitudinal	—	Language functioning post-resection, 3 groups: intact (N = 19), mild deficit (N = 19), and posterior fossa syndrome (N = 9)	—		Following tumor resection, patients with posterior fossa syndrome showed reduced FA in the left and right superior cerebellar peduncle compared to patients who did not develop language deficits. While language disturbances in posterior fossa syndrome patients resolved within months of surgery, white matter deficits in the superior

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100%), adjuvant CT (MB	Structural MRI, DTI	Cross-sectional	Ataxia, fine motor function	—	—	—	cerebellar peduncle were still evident at one year post-surgery.
Neuropsychol Rev. Author manuscript; available in PMC 2019 July 19.							Ataxia ratings were significantly higher in MB patients than in PA patients. Greater ataxia and fine motor function impairments correlated with volume loss of Cerebello-Thalamo-Cerebral (CTC) white matter pathway in MB patients, but not in PA patients. Cerebro-Ponto-Cerebellar (CPC) pathway white matter volume was significantly reduced in PA patients, but not in MB patients. Neither relationship was observed between the CPC pathway and ataxia or fine motor function. Patients with pediatric post-operative cerebellar mutism syndrome had greater ataxia and showed greater loss of volume in the CTC pathway.
y with or without focal radiation	DTI	Cross-sectional	—	Processing speed	—	—	Compared to controls and children treated with surgery/focal radiation, children with brain tumor treated with cranial-spinal radiation (CSR) show reduced integrity, indicated by significantly lower FA and greater RD, of multiple white matter tracts— particularly the optic radiations, inferior longitudinal fasciculi, and the inferior fronto-occipital fasciculi. Children treated with CSR also demonstrated lower information

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Journal of Clinical Neuropsychology	Task-based fMRI (5 tasks probing reading-related neural activation); 3 fMRI and reading evaluations at 1 year intervals.	Longitudinal	—	Reading abilities, continuous processing	—	—	processing speed scores compared to healthy controls, which was related to reduced integrity of the right optic radiations.
Journal of Clinical Neuropsychology	Task-based fMRI (grid-based spatial working memory)	Longitudinal	—	IQ, working memory, spatial span backward, attention and processing speed and showed greater reductions in reported executive dysfunction	—	—	Relative to standard-of-care, medulloblastoma patients receiving a reading intervention demonstrated altered brain activation during reading-related fMRI tasks in key areas involved in reading and language processing: left inferior frontal, temporal, ventral occipitotemporal, and subcortical regions. Improved sound awareness scores and an evident normative trend in patterns of brain activation during reading-related tasks in the intervention group highlight the potential neural and behavioral effects of preventative interventions given during medulloblastoma treatment in youth.
Journal of Clinical Neuropsychology	Task-based fMRI (grid-based spatial working memory)	Longitudinal	—	IQ, working memory, spatial span backward, attention and processing speed and showed greater reductions in reported executive dysfunction	—	—	Cancer survivors who completed the cognitive training intervention had greater improvement than wait-listed survivors on measures of working memory, spatial span backward, attention and processing speed and showed greater improvements in executive function. In the intervention group, post-intervention activation of left lateral prefrontal and bilateral medial frontal areas was

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CRT, and CT	Structural MRI (post-resection)	Cross-sectional	—	IQ, attention, working memory, and visual motor coordination	IQ, attention, working memory, and visual motor	Health-related quality of life	reduced compared to pre-intervention activation. In cerebellar tumor survivors, the quantity and extent of brain lesions after tumor resection was associated with cognitive impairments including intelligence and attention. These cognitive impairments were more apparent in MB survivors compared to PA survivors. In both groups, the extent of brain injury and related neurocognitive deficits did not impact health-related quality of life.
DTI	DTI	Cross-sectional	—	IQ, verbal reasoning, nonverbal/visual reasoning, attention, working memory, processing speed	—	—	Deficits in IQ and compromised white matter were evident in LGG patients compared to healthy controls. The effect of treatment for LGG on IQ was mediated by compromise of supratentorial white matter. Increased white matter compromise was observed in patients who presented without multiple symptoms, were not treated with surgery, were diagnosed at younger age, and whose parents had lower levels of education.
n = 17), CT and CRT (n = 5)	Task-based fMRI (letter N-back working memory)	Cross-sectional	—	Executive function, attention problems	Parent- and self-reports of social, behavioral/internalizing problems, coping responses to stressful interpersonal and peer relationships	—	Compared to healthy controls and normative data, brain tumor survivors had higher levels of psychosocial and behavioral/emotional problems. Increased activation in

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Journal of Neurological	DTI	Cross-sectional	Fine motor function/ataxia	IQ, executive function/processing speed	—	—	prefrontal and other anterior regions in response to a working memory task were correlated with higher psychosocial functioning, use of engagement coping strategies, and less use of disengagement coping strategies in patients. Use of positive coping strategies partially explained the association between behavioral/emotional functioning and brain activation.
Journal of Neurological	DTI	Cross-sectional	Fine motor function/ataxia	IQ, executive function/processing speed	—	—	In young survivors of posterior fossa tumors, significant associations were found between fronto-cerebellar tractography and intelligence as well as measures of motor function and executive function (i.e. processing speed, shifting attention). The degree of impaired fronto-cerebellar connectivity seems to underlie the extent of ataxia, fine motor dysfunction, and neurocognitive dysfunction in pediatric posterior fossa tumor survivors.
Journal of Neurological	Structural MRI	Longitudinal	—	—	—	—	High MTX exposure was associated with increased risk of leukoencephalopathy. Leukoencephalopathy was evident in all symptomatic patients and 1 in 5 asymptomatic patients, and persisted in 58% of symptomatic and 74% of asymptomatic

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Neuropsychol Rev. Author Manuscript; available in PMC 2019 July 19.	101 (fewer CNS-directed than intensive consolidation, n = 40; more CNS-directed than intensive consolidation, n = 61)	Cross-sectional	—	IQ, perceptual organization, processing speed, visuospatial integration, attention, continuous performance	—	—	patients at the end of therapy. Concurrent genome-wide association study (GWAS) revealed that polymorphisms involved in neurogenesis may contribute to susceptibility to MTX-related neurotoxicity. Leukoencephalopathy persisted in nearly 3 of 4 asymptomatic and over half of symptomatic patients at the end of therapy.
Neuropsychol Rev. Author Manuscript; available in PMC 2019 July 19.	DTI	Cross-sectional	—	IQ, visual perception/memory, attention, task-switching	—	—	While patients in both treatment groups showed significant neurocognitive deficits, significantly more p9605 patients developed leukoencephalopathy and scored below average on more neurocognitive measures. Leukoencephalopathy was detected in survivors as late as 7.7 years after end of treatment, suggesting that treatment-related white matter changes in survivors are lasting and not simply transient.
Neuropsychol Rev. Author Manuscript; available in PMC 2019 July 19.	DTI	Cross-sectional	—	IQ, visual perception/memory, attention, task-switching	—	—	Relative to controls, ALL survivors treated with modified CCG protocol performed significantly lower on all cognitive measures and survivors treated with BFM 90 protocol had lower IQ and task-switching ability. While survivors in the BFM 90 group also had lower IQ and more executive

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Neuropsychol Rev. Author manuscript; available in PMC 2019 July 19.	DTI (Baseline after surgery and before CRT, 6-month, 15-month and 27-month follow-ups after completion of CRT)	Longitudinal	—	Working memory, motor speed	—	—	function impairments than those in the BFM 83 group, no difference was found in cognitive test performance between controls and survivors treated with BFM 83. Frontal lobe FA was significantly reduced in the BFM 90 and BFM 83 groups compared to controls, but lower in the CCG group compared to all other groups.
and CRT (n = 50), Pre-CRT CT (n = 1)	Structural MRI	Cross-sectional	—	Q, working memory (behavioral measures), attention, executive function (parent ratings)	—	—	Survivors had higher overall mean ADC (i.e., more diffusion) in the hippocampus compared with controls, indicating changes in deep gray matter microstructure. Survivors also showed heightened ADC at baseline and at the 27-month follow-up, however they showed normal verbal memory performance. Visual-spatial working memory performance in survivors decreased over time compared to controls. In both groups, decreased motor speed was associated with increased ADC in the globus pallidus and putamen.
							Better working memory performance (longer digit span backwards and forwards) was positively associated with right frontal and right and left posterior NAWM volumes among brain tumor survivors. Tumor location and gender was also related to NAWM volumes.

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Journal of Clinical Neuropsychology	Resting-state fMRI	Cross-sectional	—	IQ, verbal learning, memory, reading and math fluency, executive function	—	—	Participants with infratentorial tumors had significantly greater mean NAWM volume than those with supratentorial tumors in both right and left frontal areas. Overall, males had greater mean NAWM volume compared to females. No association was found between NAWM volumes and parent ratings.
Journal of Clinical Neuropsychology	Resting-state fMRI	Cross-sectional	—	IQ, verbal learning, memory, reading and math fluency, executive function	—	—	Compared to controls, ALL survivors showed reduced resting-state functional connectivity between bilateral hippocampus, left inferior occipital, left lingual gyrus, bilateral calcarine sulcus, and right amygdala. The ALL group showed regions of functional hyperconnectivity including right lingual gyrus, precuneus, bilateral superior occipital lobe, and right inferior occipital lobe. In the ALL group, impaired cognitive function and younger age at diagnosis were associated with functional hyperconnectivity.
Journal of Clinical Neuropsychology	Structural MRI, DTI	—	—	Learning/memory	—	—	Compared to controls, the brain tumor survivor group showed reduced white matter volume, damage to the uncinate fasciculus, and a smaller right hippocampus. The hippocampus may be particularly vulnerable to the effects of treatment, as reduced

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J Child Psychol and CRT (n = 17), CT and CRT (n = 5)	Task-based fMRI (letter N-back work ing memory)	Cross-sectional	—	Executive function, attention problems, IQ, working memory, processing speed	—	—	hippocampal volume was not related to brain volume differences. Among the survivors who also underwent memory testing (n =10), memory performance was associated with measures of hippocampal volume and uncinate fasciculus. Survivors of pediatric brain tumors performed lower than controls on measures of general cognitive ability, attention, and executive function, and demonstrated altered brain activity during an fMRI working memory task. Survivors' neurocognitive deficits were associated with lower activation in bilateral frontal regions associated with sustained attention and greater activation in left cingulate regions associated with problem-solving and performance monitoring during a working memory task.
J CRT (n = 4)	Structural MRI	Cross-sectional	—	—	—	—	Brain abnormalities (i.e., leukoencephalopathy, brain atrophy, old infarcts or hemorrhages) were detected in 24% of childhood ALL survivors, with higher incidences of abnormalities occurring in survivors who received cranial radiation, had diagnoses involving the CNS, or

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	Structural MRI, DTI	Cross-sectional	Olfaction	Memory, executive function, attention, IQ		—	were classified as high-risk. Relative to controls, the ALI group showed smaller gray matter volumes of the left hippocampus, amygdala, thalamus, nucleus accumbens, left calcarine gyrus, bilateral lingual gyri and the left precuneus. ALI survivors had lower hippocampus-dependent memory scores, and lower memory scores correlated with reduced hippocampal volumes. No evidence of white matter pathology was found.
	Structural MRI (and behavioral tests) at 3 time points: (1) within the first days, (2) 3 months, and (3) 1 year after surgery.	Longitudinal	Ataxia, balance, upper limb motor function	—		—	Lesion location in pediatric cerebellar tumor patients, particularly the involvement of the deep cerebellar nuclei, was the chief predictor of later functional recovery. Cerebellar lesion volumes were significantly reduced by disappearing edema within the first 3 months post-surgery, though behavioral improvements continued for up to a year. Permanent lesions of the inferior vermis and the deep cerebellar nuclei were associated with long-lasting impairments in balance and upper limb function.
ERT, and CT	Task-based fMRI (letter N-back working memory)	Cross-sectional	—	IQ		—	Survivors of posterior fossa tumors showed typical activation

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							patterns (during a working memory task) associated with working memory in the frontal-parietal network. Higher cardiorespiratory fitness was associated with better working memory performance (behavioral) as well as more efficient neural functioning.
	Structural MRI	Cross-sectional	—	—	—	—	Relative to controls, ALL survivors show altered structural organization of large-scale brain networks, indicative of pervasive neurobiological damage. Compared to the control group, the ALL group showed significantly decreased small-world index suggesting that brain network organization is less optimal, more standardized, and more vulnerable to failure in ALL survivors.
	Task-based fMRI (continuous performance)	Longitudinal	—	IQ, attention, academic achievement, memory, verbal learning, self-esteem	—	—	Compared to healthy controls, survivors performed significantly lower on a measure of intellectual functioning and parent ratings indicated cognitive problems, inattention, and hyperactivity. In survivors, brain activation in ventral visual areas, cerebellum, supplementary motor area, and left inferior frontal cortex during a continuous performance task was diminished at baseline, and was increased at the end of a 20-session cognitive

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CT and CRT (n = 30)	Structural MRI (at end of treatment)	Longitudinal	—	IQ, attention, working memory	—	—	remediation program and at 6-month follow-up. Survivors participating in the cognitive remediation program also showed improvements between baseline and the 6-month follow-up in cognitive problems/-inattention.
	Structural MRI and SPECT	Cross-sectional	—	—	—	—	Working memory was impaired compared to norms for the total sample and the standard-/high-risk group. Leukoencephalopathy in survivors was predictive of lower total digit span, an important indicator of working memory.
	Structural MRI	Cross-sectional	—	IQ, verbal comprehension, working memory, processing speed, perceptual reasoning, executive function, verbal and visual declarative memory, visual-spatial processing, visual attention	—	—	White matter changes were detected by MRI in 7% (n = 3) of ALL survivors, who had all received CRT. MR SPECT revealed changes in 1H-MRS metabolite ratios in 29% (n = 13) of survivors and decreased mean NAA/Cr ratio in survivors who received CRT. ALL survivors had significantly reduced white matter volume compared to controls, however, the groups did not differ on measures of gray matter or whole brain volumes. Observed white matter differences were particularly evident in the left caudate/left corpus callosum, right caudate, bilateral

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Journal of Neurosurgery	Task-based fMRI (letter N-back working memory)	Cross-sectional	—	IQ, working memory, processing speed, verbal and nonverbal executive functioning	—	—	thalamus, fornix and bilateral superior fronto-occipital fasciculus. ALL survivors performed significantly lower than controls on neurocognitive measures of processing speed, working memory, and verbal memory. These cognitive performance deficits were not related to any regional nor whole brain volume differences.
Journal of Neurosurgery	Task-based fMRI (letter N-back working memory)	Cross-sectional	—	IQ, working memory, processing speed, verbal and nonverbal executive functioning	—	—	Compared to controls, ALL survivors performed less accurately on a working memory task and displayed greater activation in brain areas associated with working memory (dorso- and ventro-lateral prefrontal cortex) and error monitoring (anterior cingulate cortex). These findings align with the theory of compensatory activation in relevant brain regions, suggesting that increased cognitive effort is required to complete tasks in pediatric ALL survivors.
Journal of Neurosurgery	DTI	Cross-sectional	Motor speed	IQ, verbal comprehension, perceptual organization, processing speed	—	—	In survivors of childhood ALL and medulloblastoma, mean white matter FA was significantly reduced compared to controls, and specifically within the right inferior fronto-occipital fasciculus (IFO) and genu of the corpus callosum (gCC). Processing speed was

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Journal of Clinical Neuropsychology	Structural MRI, SPECT	Longitudinal	—	IQ, executive function, language, verbal fluency, concentration, memory, praxis			correlated with white matter FA in the splenium (sCC) and body of the corpus callosum (bCC); motor speed was related to white matter FA in the right IFO.
Journal of Clinical Neuropsychology	Structural MRI, SPECT	Longitudinal	—	IQ, executive function, language, verbal fluency, concentration, memory, praxis		Emotional coping, social adjustment	Following brain tumor resection, patients developed language and motor deficits, neurocognitive problems with executive function, concentration, and visuo-spatial attention, and behavioral and affective disturbances. Post-surgical mutism was linked to perispratial deficits in supratentorial regions involved in language dynamics, syntax, naming, executive functioning, affective regulation, and behavior.
Journal of Clinical Neuropsychology	Structural MRI (at baseline after induction therapy and after end of consolidation therapy)	Longitudinal	—	—	—	—	During treatment for ALL, patients developed WM hyperintensities involving the anterior, posterior, and superior corona radiata and superior longitudinal fasciculus fiber tracts. T2 signal intensity in these regions was greater on the second examination for all patients, with greater increases evident in older patients, who were treated with more intense CT.
Journal of Clinical Neuropsychology	Structural MRI	Cross-sectional	—	IQ, language, attention, memory, processing speed, executive function, academic achievement, visual-constructional skills	—	—	Compared to controls, ALL survivors showed reduced white matter in the right frontal lobes.

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
							Also relative to controls, survivors showed lower performances on tests of attention, visual-constructional skills, mental flexibility, and math achievement. While no regional gray matter volume differences were found between the groups, decreased performance on neuropsychological measures was related to reduced regional white matter volumes in survivors.
	Structural MRI (post-resection)	Cross-sectional	—	IQ, continuous performance, phonological processing, verbal fluency, fine motor coordination, verbal working memory	—	—	Cerebellar pilocytic astrocytoma patients did not differ from controls on neuropsychological tests of verbal fluency, animal naming, attention, phonological processing, or fine motor control- but did have significantly lower IQ scores. Damage to left hemispherical cerebellum lobule VIII was significantly correlated with reduced digit span for auditory (but not visual) stimuli in patients, who scored lower on these measures compared with controls. In patients, damage to the vermis and hemispherical lobule IV/V bilaterally was associated with decreased effects of articulatory suppression.
	Structural MRI	Cross-sectional	—	—	—	—	Brain tumor survivors showed reduced gray matter density in the thalamus and entorhinal cortex and reduced white matter density in

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
CT	DTI	Cross-sectional	—	—	—	—	the internal capsule, hypothalamus, corpus callosum, and cuneus of the occipital lobe, compared to healthy sibling controls. Compared with controls, frontal lobe and parietal lobe white matter FA were significantly less in MB survivors - with a larger difference in frontal lobe FA compared with the parietal lobe. This difference suggests that compared to the parietal lobe, frontal lobe white matter may be more sensitive to effects of cranial irradiation treatment.
CT and CSI (n = 9) MB	DTI	Cross-sectional	—	IQ (full-scale, verbal, performance)	—	—	There were no significant differences in IQ scores across patient groups. Percent of difference in white matter FA for each patient was compared with the age-matched control group. Within survivors, the FA difference score was significantly correlated with all three measures of IQ (full-scale, verbal, performance), even after adjusting for age at treatment, irradiation dose, and time since completion of treatment.
CSF, and adjuvant CT	DTI	Cross-sectional	—	IQ	—	—	In MB patients, reduced IQ was associated with reduced white matter integrity (increased apparent diffusion coefficient decreased FA). Altered white matter was evident in

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
Journal of the American Academy of Child and Adolescent Psychiatry	DTI before the end of radiotherapy and at 3 months, 6 months and 1 year after completion of radiotherapy.	Longitudinal	—	—	—	—	the CSR group compared to controls—with increased apparent diffusion coefficient in all regions and lower FA in the genu of the corpus callosum, the anterior and posterior regions of the internal capsule, and inferior and high frontal white matter.
Neuropsychol Rev.	DTI before the end of radiotherapy and at 3 months, 6 months and 1 year after completion of radiotherapy.	Longitudinal	—	—	—	—	Across scans, increasing reduction in mean FA over treatment for medulloblastoma was correlated with increasing radiation dose up to 45 Gy-at which point this trend reversed and mean FA approached baseline value. In both patients, more severe mean FA reduction was evident in the frontal lobes compared to the parietal lobes despite both brain regions being exposed to the same radiation dose. After cranial radiation, mean FA increase in the brainstem was also shown in both patients.
Journal of the American Academy of Child and Adolescent Psychiatry	Structural MRI	Cross-sectional	—	IQ, attention, academic achievement	—	—	ALL survivors performed significantly lower on most neurocognitive measures compared to normative test scores, with cranial irradiation-treated survivors performing lower than those treated with CT only. Both survivor groups had significantly reduced white matter volumes compared to sibling controls, and survivors treated with

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
Journal of Clinical Neuropsychology	Structural MRI (at start of therapy and again 2 years later)	Longitudinal	—	—	—	—	cranial irradiation had significantly smaller white matter volumes than survivors treated with CT alone. Additionally, smaller white matter volumes in ALL survivors were related to greater deficits in intelligence, attention and academic achievement.
	Structural MRI	Cross-sectional	—	Motor and cognitive performance, postural control, working memory	—	—	Compared to medulloblastoma patients with increased NAWM volume following treatment, those with decreased NAWM volume showed significantly increased fractal features and NAWM boundary irregularities. In patients with decreased NAWM volume, fractal features were highly correlated with NAWM volume after treatment.
Journal of Clinical Neuropsychology	Structural MRI	Cross-sectional	—	Motor and cognitive performance, postural control, working memory	—	—	Overall, cerebellar tumor patients did not differ from controls on cognitive measures; working memory was only impaired in patients who had received CT or RT after surgical resection. Patients with abnormal posture who did not receive CT or RT had brain lesions containing the fastigial and interposed nuclei (NF and NI), whereas patients with normal posture did not have lesions containing these nuclei. Age at surgery, time since surgery or lesion volume were not significant predictors of

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
and CSI (n = 52), adjuvant CT (n	Structural MRI	Longitudinal	—	—	—	—	motor or cognitive recovery. Patients treated for MB at younger ages demonstrated reduced development of NAWM volume, compared to healthy controls. Younger age at irradiation and placement of a shunt were significantly associated with reduced NAWM volume in patients. Over a period of 4–5 years, differences in NAWM and CSF volume between patients who had shunts and those without, resolved. With additional courses of CT, the amount of white matter impacted by treatment and the severity of leukoencephalopathy increased in both (low- and standard/high-risk) ALL groups. Importantly, both the severity and extent of leukoencephalopathy significantly decreased 1.5 years after completion of treatment. Increasing exposure to CT (increased dose, additional courses) was associated with increased severity of leukoencephalopathy in ALL. The prevalence of leukoencephalopathy was significantly reduced ~1.5 years after the completion of CT.
	Structural MRI (4 times throughout treatment)	Longitudinal	—	—	—	—	
	Structural MRI (4 times throughout treatment)	Longitudinal	—	—	—	—	

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
n = 16; CRT alone (n = 3), CT and CT (n = 5)	Task-based fMRI (visual stimulation)	Cross-sectional	—	—	—	—	During a visual stimulation task, childhood cancer survivors showed smaller activation volume in the primary visual cortex relative to healthy controls. Brain tumor survivors showed significantly smaller activation volume compared to both ALL survivors and healthy controls. While these results indicate that BOLD fMRI is a feasible method to investigate brain function in childhood cancer survivors, future functional neuroimaging studies should account for effects of quantitative differences in the BOLD responses of survivors as compared to healthy subjects.
whole brain irradiation, CT	Structural MRI	Cross-sectional	—	Visual and verbal long-term memory	—	—	ALL survivors did not differ from controls on measures hippocampal volume nor long-term memory performance, and hippocampal volumes were not related to measures of long-term memory.
	DTI	Cross-sectional	—	—	—	—	Compared to controls, MB survivors displayed significantly reduced FA in temporal, parietal, and occipital periventricular white matter, corpus callosum, and corona radiata.
and CSI (n = 37), CT (n = 18)	Structural MRI	Cross-sectional	—	IQ, continuous performance/attention	—	—	Compared to norms, child brain tumor survivors showed intellectual and related attentional deficits.

Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
and CT	Structural MRI (mean num. scans per patient = 6, up to 5 years after treatment)	Longitudinal	—	—	—	—	Greater attentional deficits were associated with reduced NAWM, particularly within the frontal lobe/prefrontal area and cingulate gyrus. Both right and left hippocampal volumes continually decreased after medulloblastoma treatment until approximately 2–3 years after diagnosis, when hippocampal volumes resumed a normal positive growth pattern. Hippocampal volume loss occurred mainly in the posterior regions, and was associated with female sex, low parental education, shunt placement, and positive seizure history.
CT and CRT (n = 4), CRT and ion (n = 1)	Structural MRI and SPECT (0, 8, and 20 weeks and 1, 2, and 3 years after diagnosis)	Longitudinal	—	—	—	—	Metabolite changes in the brain after treatment of childhood ALL were detected, although simultaneous structural white matter abnormalities were not observed: 81% of patients showed metabolite changes while only 23% showed white matter changes at 20 weeks.
CSI, CT	DTI	Cross-sectional	—	Intellectual outcome (school performance)	—	—	With the exception of frontal periventricular white matter, FA was significantly reduced in medulloblastoma patients compared to controls in all anatomical sites (including posterior fossa and supratentorial white matter).

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
SI (n = 9)?	Perfusion MRI at end of treatment (n = 19), and SPECT (n = 17)	Cross-sectional	—	—	—	—	Decreased supratentorial white matter FA was associated with younger age at treatment, longer interval since treatment, and decline in school performance. In children treated for ALL, small brain defects were detected by SPECT in 29% of children in the left basal, frontal or temporal areas, whereas perfusion MRI showed no focal perfusion defects.
n = 40, whole-brain irradiation only (n = 16), CTR (n = 18)	Structural MRI	Cross-sectional	—	IQ, attention, memory, academic achievement	—	—	Brain tumor demonstrated impaired neurocognitive test performance on all measures. NAWM volumes were associated with both attentional abilities and IQ, with a significant amount of the relationship between NAWM and IQ explained by attentional ability. These results suggest that reduced NAWM among pediatric brain tumor patients contributes to declining IQ and academic achievement because of its detrimental effect on attention. In contrast to normal development, the total midsagittal corpus callosum area of medulloblastoma patients decreased as time since cranial-spinal radiation increased. Additional declines in
CT	Structural MRI (multiple times over 4-yr period)	Longitudinal	—	—	—	—	

Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
Journal of Neurology, Neurosurgery, and Psychiatry (n = 42), CT (n = 29)	Structural MRI	Cross-sectional	—	IQ, verbal memory, and sustained attention	—	—	area were also observed in the genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium with the greatest deviations from typical development occurring at the isthmus and the splenium. These subregions of the corpus callosum, which normally have a high rate of growth in childhood, are impacted by the high dose of irradiation that they are exposed to in the treatment of pediatric MB.
							Neurocognitive performance in MB survivors was below age-related norms. Younger age at CRT was related to lower performance on all neurocognitive tests with the exception of verbal memory, while increased time since completion of CRT was correlated with lower performance on all neurocognitive tests except sustained attention. A significant amount of the association between age at CRT and neurocognitive measures (IQ, factual knowledge, verbal and nonverbal thinking) was accounted for by NAWM.
	Structural MRI (post-resection)	Cross-sectional	—	Executive function (incl. planning and sequencing), visual-spatial function, expressive language, verbal memory	Parent and clinician report of behavioral problems, regulation of affect		Cerebellar tumor survivors exhibited impaired executive function, visual-spatial function, expressive

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
n = 15)	Structural MRI (At least 4 scans from beginning to end of treatment, n = 26)	Longitudinal	—	Attention, language, motor and sensory functions, visuospatial function, memory and learning, IQ, concentration, inhibition and control	—	—	language, verbal memory and modulation of affect. Particularly, lesions of the vermis were associated with dysregulation of affect. Older survivors showed more behavioral deficits than younger survivors.
or reduced dose) and CT	Structural MRI	Longitudinal	—	—	—	—	Transient white matter hyperintensities (prominent in frontal lobes) were noted in patients during treatment for ALL with CT only (n = 3), who were significantly younger than those without highintensity white matter changes. Except for deficits of attention and functions directly dependent upon frontal areas, white matter changes were not correlated with neuropsychological tests.
ion and CSI (n = 9), surgical CT (n = 9), PF: surgery alone	Structural MRI (T1, T2, PD [proton density])	Cross-sectional	—	IQ (full-scale, verbal, performance)	—	—	MB patients treated with cranial-spinal radiation have significant loss of NAWM volume. There were no significant differences in the rate of NAWM volume loss based on age at cranial-spinal radiation, however, the rate of NAWM volume loss was significantly slower in children receiving reduced-dose cranial-spinal radiation
							Childhood MB survivors treated with cranial radiation (with or without CT) had significantly reduced

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
CT and CRT (n = 17)	Structural MRI (first at end of treatment, second 5 years later)	Longitudinal	—	IQ, attention, language, motor/sensory/visuospatial function, memory	—	—	NAWM and lower full-scale IQ scores compared to PF survivors treated with surgery alone. Further, decreased NAWM in MB survivors following was associated with lower full-scale IQ.
							Overall, treatment-related brain abnormalities (e.g. high-intensity white matter changes, cortical atrophy, calcifications) were detected in 25% of ALL patients post-treatment. Neuropsychologic test results did not significantly differ between patients with brain abnormalities and patients with normal MRI findings, however patients with persistent white matter changes (n = 2) had reductions in verbal function.
CT and/or CT	Structural MRI	Cross-sectional	—	—	—	—	Within brain tumor survivors, brain parenchyma and white matter volumes significantly decreased as atrophy increased (as graded by radiologists). Gray matter volumes had no relationship with atrophy. Patients who received surgery, irradiation, and chemotherapy did not show differences in brain parenchyma, white matter, and gray matter volumes relative to patients treated with surgery and irradiation alone. Patients who received surgery and irradiation demonstrated

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Journal	Sample size (N)	Patients/Survivors (n)	Typically-developing controls (n)	Type of cancer	Survivor age at time of study in years (mean, SD, [range])	Age at diagnosis/treatment in years (mean, SD, [range])	Time since diagnosis/treatment conclusion in years (mean, SD, [range])
							reduced white matter volumes relative to patients treated with surgery alone.

lastic leukemia; PA, pilocytic astrocytoma; MB, medulloblastoma; PNET, primitive neuroectodermal tumor; WM, white matter; NAWM, normal appearing white matter; therapy; CRT, cranial radiation therapy; IV-MTX, intravenous methotrexate; CSI, craniospinal irradiation; BMT, bone marrow transplant; DTI, diffusion tensor imaging; imaging; SPECT, single-photon emission computed tomography; DWI, diffusion weighted imaging; ASL, arterial spin labelling; IQ, intelligence quotient; FA, diffusion coefficient; CBF, cerebral blood flow.

Table 2

Review of neuroimaging studies in adult survivors of pediatric cancer

First author	Year of publication	Journal	Sample size (N)	Survivors (n)	Healthy controls (n)	Age at assessment (years)	Age at diagnosis in years (mean, SD, [range])	Time since diagnosis/treatment in years (mean, SD, [range])	Type of cancer
1 Chen et al.	2016	Neuroimage Clinical	32	16	16	22.5 (5.2) [17-34]	7.6 (5.1)	14.9 (7.3)	Cerebellar tumor
2 Tammes et al.	2015	Pediatric Blood and Cancer	260	130	130	29.3 (7.3) [18.6-46.5]	6.2 (4.0) [0.3-16.0]	23.0 (7.7) [7.4-40.0]	ALL
3 Jayakar et al.	2015	Neuropsychology	94	35	59	24.10 (4.93) [17-36]	8.17 (4.43) [1.17]	15.38 (5.34) [5.24]	Brain tumor (posterior fossa, pituitary, frontal, temporal, other)
4 King et al.	2015b	PLOS ONE	54	27	27	22.7 (4.5) [18-32]	9.0 (5.14)	13.7 (5.37)	Brain tumor (posterior fossa, temporal, occipital, hypothalamic, third ventricle)
5 King et al.	2015a	Journal of the International Neuropsychological Society	34	17	17	23.2 (5.9) [17-35]	7.65 (4.90) [1.17]	15.5 (7.6) [4.5-30]	Posterior fossa brain tumor
6 Smith et al.	2014	Neuropsychology	37	18	19	24.19 (4.51) [19-40]	7.22 (4.57) [1.17]	17.13 (5.43) [5.25]	Brain tumor (n = 6 MB n = 1 pineoblastoma, n = 9 astrocytoma, n = 1 ganglioglioma, and n = 1 craniopharyngioma). Location of tumor: n = 13 in posterior fossa, n = 1 parietal lobe, n = 1 occipital
7 Edelmann et al.	2014	Brain	98	75	23	CT alone: 24.9 (3.6), CRT: 26.7 (3.4)	CT alone: 9.97 (3.99), CRT: 2.81 (1.73)	CT alone: 15.0 (1.7), CRT: 23.9 (3.1)	ALL
8 Schuite ma et al.	2013	Journal of Clinical Oncology	142	93	49	CRT and CT: 31.2 (4.8), CT: 26.7 (5.1)	CRT and CT: 5.7 (3.7), CT: 5.3 (3.5)	CRT and CT: 25.4 (3.2), CT: 21.4 (2.9)	ALL, lymphoma
9 Zeller et al.	2013	Journal of Clinical Oncology	260	130	130	28.4 [18.6-46.5]	5.3 [0.3-15.9]	22.5 [7.4-40.0]	ALL
10 Edelmann et al.	2013	Pediatric Blood and Cancer	38	38	—	Without dex: 24.6 [20.4-32.4], with dex: 24.6 [19.7-31.2]	Without dex: 8.7 [3.8-16.9], with dex: 11.8 [5.8-18.6]	Without dex: 15.9 [14.8-17.9], with dex: 13.3 [12.0-15.1]	ALL
11 Monje et al.	2013	Pediatric Blood and Cancer	20	10	10	30.8 [22-40]	10.2 [1.83-17.0]	Not stated	ALL

First author	Year of publication	Journal	Sample size (N)	Survivors (n)	Healthy controls (n)	Age at assessment (years)	Age at diagnosis in years (mean, SD, [range])	Time since diagnosis/treatment in years (mean, SD,	Type of cancer
12 Armstrong et al.	2013	Journal of the National Cancer Institute	85	85	—	36.7 (6.4)	6.6 (4.1)	30.1 (6.2)	ALL
13 Krull et al.	2012	Journal of Clinical Oncology	62	62	—	42.2 (4.77) [1855]	15.1 (3.30)	>= 15	Hodgkin lymphoma
14 Brinkman et al.	2012	Neuro-oncology	20	20	—	29 [21–36]	[2–17]	18 [12–25]	MB
15 Dellamini et al.	2008	Journal of Magnetic Resonance Imaging	27	13	14	17–37	2–16	16–23	ALL
16 Porto et al.	2008	European radiology	41	20 (n=10 male, n=10 female)	21	Male: 22.0 (3.2) [18–28], Female: 23.2 (3.5) [18–27]	Male: 8.1 (3.8) [2.2–13.7], Female: 8.1 (3.8) [3.0–13.3]	Not stated	

First author	Type of treatment	Neuroimaging modalities	Type of study	Physical and physiological outcome measures	Cognitive and behavioral outcome measures	Emotional and quality of life measures	Main findings
1 Chen et al.	Surgical resection (n = 16), CT (n = 7), CRT (n = 8)	Resting-state fMRI	Cross-sectional	—	—	—	Pediatric brain tumor survivors showed altered rsFC in frontal functional networks (executive control, salience, default mode) compared to controls. Even at rest, survivors' hyperconnectivity in frontal functional networks may reflect recruitment of more brain regions due to continuous needs of a higher level of cognitive effort ("all hands on deck" approach).
2 Tammes et al.	CT (n=130), CT and CRT (n=18), CT and stem-cell transplantation (n=3)	Structural MRI	Cross-sectional	—	Executive functioning	—	ALL survivors had smaller surface area in several cortical regions but reduced cortical thickness in only one region, compared to controls. Cortical surface area/thickness in these regions was not associated with disease or treatment variables. In survivors, reduced cortical surface area in prefrontal regions was associated with more self-reported problems in executive functioning (particularly difficulties in emotional control and self-monitoring).
3 Jayakar et al.	Surgical resection (n=35), CT (n=12), CRT (n=16)	Structural MRI	Cross-sectional	—	Verbal memory, IQ	—	Compared to controls, brain tumor survivors had lower hippocampal, putamen, and whole brain volumes as well as lower verbal memory scores (auditory attention list span and final list learning). Hippocampal volume in survivors was significantly correlated with auditory attention. In both groups,

First author	Year of publication	Journal	Sample size (N)	Survivors (n)	Healthy controls (n)	Age at assessment (years)	Age at diagnosis in years (mean, SD, [range])	Time since diagnosis/treatment in years (mean, SD,	Type of cancer
4 King et al.	CRT with CT (n=11), CRT without CT (n=3), no CRT (n=12), CT and no CRT (n=1)		Structural MRI, DTI	Cross-sectional	—	IQ	—	hippocampal and putamen volumes were significantly correlated with each other but not with total brain volume.	Brain tumor survivors treated with CRT had lower IQ and a lower level of white matter integrity relative to survivors without CRT and healthy controls. Non-CRT treated survivors had lower mean FA compared with healthy controls. IQ and cumulative neurological factors were related to white matter disruption in the CRT-treated group of survivors.
5 King et al.	Neurosurgery (n=17), CT (n=8), CRT (n=9)		Task-based fMRI (N-back paradigm)	Cross-sectional	—	Working memory, IQ	—	Survivors of childhood posterior fossa brain tumors had lower IQ scores and working memory performance compared with controls. Among survivors, increased prefrontal activation (left superior/middle frontal gyr) during a working memory task was associated with increased working memory demands and reduced working memory performance.	Survivors of childhood posterior fossa brain tumors had lower IQ scores and working memory performance compared with controls. Among survivors, increased prefrontal activation (left superior/middle frontal gyr) during a working memory task was associated with increased working memory demands and reduced working memory performance.
6 Smith et al.	Surgical resection (n = 18), CT and CRT (n = 8), CT (n = 1), and CRT (n = 1)		DTI	Cross-sectional	—	Reading achievement, processing speed, skilled motor speed	—	Among brain tumor survivors and controls, white matter FA values of the parietotemporal-occipitotemporal (PT-OT) tract were associated with word reading, and FA values in the inferior fronto-occipital fasciculus (IFOF) were associated with reading in survivors only. Among survivors only, processing speed mediated the relation between white matter FA (in PTOT and IFOF) and word reading skill.	Among brain tumor survivors and controls, white matter FA values of the parietotemporal-occipitotemporal (PT-OT) tract were associated with word reading, and FA values in the inferior fronto-occipital fasciculus (IFOF) were associated with reading in survivors only. Among survivors only, processing speed mediated the relation between white matter FA (in PTOT and IFOF) and word reading skill.
7 Edelmann et al.	CT alone (n=36), CT and CRT (n=39)		Structural MRI, DTI	Cross-sectional	—	IQ, academic performance, attention, memory, processing speed, executive function	—	CRT-treated ALL survivors performed lower than survivors treated with CT alone on only 3 of 20 neurocognitive measures. Compared to healthy controls, ALL survivors had lower neurocognitive performance, reduced gray and white matter, and higher FA in fibre tracts within the left hemisphere. Frontal and temporal lobe volumes correlated with vocabulary and academic ability; frontal, parietal, and temporal white matter volumes were associated with memory. Higher FA in the left longitudinal fasciculus and left uncinate fasciculus were associated with lower memory and learning performance. Increased FA in the left sagittal stratum was associated with better sustained attention	CRT-treated ALL survivors performed lower than survivors treated with CT alone on only 3 of 20 neurocognitive measures. Compared to healthy controls, ALL survivors had lower neurocognitive performance, reduced gray and white matter, and higher FA in fibre tracts within the left hemisphere. Frontal and temporal lobe volumes correlated with vocabulary and academic ability; frontal, parietal, and temporal white matter volumes were associated with memory. Higher FA in the left longitudinal fasciculus and left uncinate fasciculus were associated with lower memory and learning performance. Increased FA in the left sagittal stratum was associated with better sustained attention
8 Schuite ma et al	CT (n=49), CT and CRT (n=44)		DTI	Cross-sectional	—	IQ, speed and accuracy of	—	Compared with controls, ALL and lymphoma survivors treated with CRT	Compared with controls, ALL and lymphoma survivors treated with CRT

First author	Year of publication	Journal	Sample size (N)	Survivors (n)	Healthy controls (n)	Age at assessment (years)	Age at diagnosis in years (mean, SD, [range])	Time since diagnosis/treatment in years (mean, SD,	Type of cancer
9 Zeller et al.	CT (n=130), CT and CRT (n=18), CT and stem-cell transplantation (n=3)		Structural MRI	Cross-sectional	—	information processing, attention, working memory	—	showed decreased FA in frontal, parietal, and temporal WM tracts. Decreased FA was associated with poorer neuropsychological performance. Trends for lower WM FA were seen in the CT-treated survivors. Similarly, CRT-treated survivors performed significantly lower on all neuropsychological measures compared to controls whereas survivors treated with CT alone did not differ significantly from controls. Reduced WM integrity in CRT-treated survivors was associated with younger age at CRT and higher dosage.	
10 Edelmann et al.	CT (n=20 with prednisone and no dexamethasone, n=18 with dexamethasone)		Structural MRI, task-based fMRI (memory recognition tasks: word & face)	Cross-sectional	—	IQ, processing speed, executive function, verbal learning/memory	—	ALL survivors showed smaller volumes of cortical gray matter, cerebellar white matter, amygdala, caudate, hippocampus, thalamus, and intracranial volume compared with controls – with the strongest effect found in the caudate. These neuroanatomic volumes were not affected by age at diagnosis nor treatment variables. Survivors also showed reduced processing speed, executive function, and verbal learning/memory in survivors compared with controls. Reduced neurocognitive performance correlated with smaller volumes of cortical gray matter, caudate, and thalamus and intracranial volume in survivors	
11 Monje et al.	CT and CRT (n=10)		Structural MRI; task-based fMRI (memory encoding task)	Cross-sectional	—	Recognition memory	—	Compared to survivors treated with only prednisone (without dexamethasone), ALL survivors treated with dexamethasone had lower performance on several memory-dependent measures including story memory and word recognition. Decreased neural activation in the left retrosplenial brain region was associated with dexamethasone treatment; story memory was associated with altered activation in left inferior frontal-temporal brain regions.	
								Compared to healthy controls, ALL survivors demonstrated lower recognition memory, greater hippocampal atrophy and altered memory-related hippocampal activation. Survivors showed increased neural activation in several brain regions during unsuccessful memory encoding, which may reflect ineffective compensatory neural recruitment.	

First author	Year of publication	Journal	Sample size (N)	Survivors (n)	Healthy controls (n)	Age at assessment (years)	Age at diagnosis in years (mean, SD, [range])	Time since diagnosis/treatment in years (mean, SD,	Type of cancer
12 Armstrong et al.	CT (n=85), 24 Gy CRT (n=36), 18 Gy CRT (n=49)		Task-based fMRI (memory task), DTI	Cross-sectional	—	Memory, IQ, cognitive status	—	ALL survivors who received 24 Gy (but not 18 Gy) CRT had reduced cognitive status and memory performance. The mean score for long-term narrative memory among survivors who received 24 Gy CRT was equivalent to that for individuals older than 69 years. Memory impairments were associated with smaller temporal lobe white matter volumes, thinner parietal and frontal cortices, increased radial diffusivity (inverse measure of WM integrity) in parietal and temporal lobes, and reduced hippocampal volume. Neural activation during memory retrieval in the left anterior hippocampus was correlated with design memory impairment in all survivors, and was driven by the 24 Gy rather than the 18 Gy group. Neural activation during	
13 Krull et al.	CT and thoracic radiation		Structural MRI	Cross-sectional	—	IQ, attention, memory, processing speed, executive function	—	Lymphoma survivors showed lower performance on sustained attention, short-term memory, long-term memory, working memory, naming speed, and cognitive fluency compared with age-adjusted norms. Leukoencephalopathy was present in 53% of survivors, who demonstrated lower cognitive fluency than those without leukoencephalopathy. Evidence of cerebrovascular injury was present in 37% of survivors.	
14 Brinkman et al.	CRT (n=20), CT (n=15)		Structural MRI, DTI	Cross-sectional	—	IQ, academic skills, memory, attention, processing speed, motor function, executive function	—	IQ in medulloblastoma survivors was lower than population norms, and 75% of survivors showed executive function impairment. Lower performance on executive function tasks was correlated with reduced white matter integrity in multiple brain regions. Radial diffusivity in the frontal lobes was correlated with shifting attention and cognitive flexibility, whereas volume and cortical thickness were not correlated with neurocognitive function. Neurocognitive impairment was common and involved many domains.	
15 Dellani et al.	Total brain radiation (18–24 Gy) and CT		DTI	Cross-sectional	—	—	—	ALL survivors had significantly reduced white matter FA values in the temporal lobes, hippocampi, and thalami along with significant white matter volume loss. Although survivors did not show reductions in gray matter, they did show decreased total brain volume and intracranial volume compared to controls. Concerning structural	

First author	Year of publication	Journal	Sample size (N)	Survivors (n)	Healthy controls (n)	Age at assessment (years)	Age at diagnosis in years (mean, SD, [range])	Time since diagnosis/treatment in years (mean, SD,	Type of cancer
16 Porto et al.	CT (n = 10), CT and CRT (n = 10)		Structural MRI, DTI	Cross-sectional	—	—	—	white matter changes (as indexed by global and frontal WM mean diffusivity), adult survivors of childhood ALL show the same age dependence as controls - no age dependence of radiation damage was found. Compared to controls, ALL survivors showed reduced white matter FA, with the most severe effects apparent in those who had received both CRT and CT (compared to CT alone). Survivors treated with CRT had reduced WM volumes and gray matter concentration within the caudate nucleus and thalamus.	

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Abbreviation: ALL, acute lymphoblastic leukemia; PA, pilocytic astrocytoma; MB, medulloblastoma; PNET, primitive neuroectodermal tumor; WM, white matter; NAWM, normal appearing white matter; LGG, low-grade glioma; CT, chemotherapy; CRT, cranial radiation therapy; IV-MTX, intravenous methotrexate; CSI, craniospinal irradiation; BMT, bone marrow transplant; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; SPECT, single-photon emission computed tomography; DWI, diffusion weighted imaging; ASL, arterial spin labelling; IQ, intelligence quotient; FA, fractional anisotropy.