Review

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International Journal of Hematologic Oncology

Pediatric cancer, posttraumatic stress and fear-related neural circuitry

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Practice points

- With more children surviving pediatric cancer today than ever before, there is an increased emphasis on optimizing psychosocial outcomes.
- A significant subset of children with cancer will experience cancer-related posttraumatic stress symptoms (PTSS) and disorder (PTSD), which can lead to long-term impairment.
- Recent neuroimaging studies provide novel insights into biological mechanisms leading to the development of PTSS/PTSD and may provide novel targets for the prevention or treatment of PTSS/PTSD in pediatric cancer populations.
- Neuroimaging studies show structural and functional alterations in fear neural circuitry in childhood cancer patients and survivors, which may contribute to the development of PTSS/PTSD in some youth.
- New neurobiological insights may guide the development of targeted interventions for children with cancer to prevent the development and/or maintenance of PTSS.
- Screening and referrals of children and families for cancer-related PTSS and other concurrent stressors is critical for optimizing mental health throughout treatment and survivorship.

Thisreview examines the neurobiological effects of pediatric cancer-related posttraumatic stress symptoms (PTSS). We first consider studies on prevalence and predictors of childhood cancer-related PTSS and compare these studies to those in typically developing (i.e., noncancer) populations. Then, we briefly introduce the brain regions implicated in PTSS and review neuroimaging studies examining the neural correlates of PTSS in noncancer populations. Next, we present a framework and recommendations for future research. In particular, concurrent evaluation of PTSS and neuroimaging, as well as sociodemographic, medical, family factors, and other life events, are needed to uncover mechanisms leading to cancer-related PTSS. We review findings from neuroimaging studies on childhood cancer and one recent study on cancer-related PTSS as a starting point in this line of research.

First draft submitted: 27 February 2019; Accepted for publication: 15 May 2019; Published online: 11 July 2019

Keywords: acute lymphoblastic leukemia • amygdala • anterior cingulate cortex • childhood cancer • childhood leukemia • hippocampus • neural development • neuroimaging • posttraumatic stress disorder • prefrontal cortex

Substantial achievements in the treatment of childhood cancers, particularly childhood leukemias, have fortunately resulted in a dramatic increase in survival rates. What was once a death sentence is now nearing 90% survival for some forms of childhood cancer [1]. With more children surviving these experiences, however, increasing emphasis has been placed on longer-term psychosocial outcomes [2]. A growing body of research indicates that posttraumatic stress disorder (PTSD) and symptoms (PTSS) are some of the most important psychological consequences for those affected by childhood cancer, as well as, their parents and siblings. PTSD is a debilitating and often chronic

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mental disorder that develops in a subset of individuals following a trauma. In children and adolescents, PTSS may include reexperiencing traumatic aspects of childhood cancer, avoidance of reminders, and cognitive, emotional and physical symptoms such as heightened arousal and memory problems. Interestingly, rates of PTSD do not appear to be elevated among childhood cancer populations compared with the general population (4.7 to 21%). However, subclinical levels of PTSS are extremely common (e.g., up to 73.3%) [3,4] in child, adolescent, and adult survivors and have important implications. Indeed, subsyndromal PTSS can greatly reduce quality of life, limit educational and occupational achievement, and impair medical outcomes [5,6]. Childhood cancer-related PTSS are associated with psychiatric comorbidity and neurocognitive deficits [5,6].

The fact that most children adjust psychologically well to cancer is consistent with studies on rates of PTSS/PTSD following exposure to other potentially traumatic events in childhood (e.g., interpersonal violence, accidents, natural disasters, injuries). That is, although a majority of individuals will experience one or more traumatic events before their 18th birthday [7], only a small fraction will subsequently develop PTSD (8–10%) [8]. Nonetheless, exposure to childhood trauma remains one of the most potent risk factors for the development of trauma-related symptomology throughout the life course. This suggests that the exposure itself may fundamentally change the child's biology in a way that increases vulnerability to the expression of PTSS/PTSD. Indeed, a growing body of research using advanced brain imaging methods demonstrates structural and functional changes in the developing brain following exposure to childhood trauma, even in the absence of PTSS/PTSD. Further, dysfunction in certain brain areas is associated with the expression of PTSD or certain PTSS dimensions (e.g., re- experiencing). In these contemporary neurobiological models of childhood trauma, the brain represents an important mediator, explaining the link between trauma and the development of PTSS/PTSD. Over the past two decades, there has been a rise in structural and functional magnetic resonance imaging (MRI) studies on pediatric PTSS/PTSD. These studies have revealed abnormalities in the structure and function of brain regions and networks that support a range of cognitive and emotion-related functions including attention, reward processing, emotion regulation and threat processing. Neuroimaging studies provide novel insights into biological mechanisms leading to the development of psychopathology and may provide novel targets for the prevention or treatment of pediatric PTSS/PTSD.

Importantly, neuroimaging studies on pediatric PTSS/PTSD have focused almost exclusively on exposure to natural disasters (e.g., earthquakes) or interpersonal violence. Despite the significant number of children diagnosed with pediatric cancer and other life-threatening illnesses each year, little is known about neurobiological mechanisms leading to the expression of PTSS in these populations. Cancer-related changes in underlying neurobiology may reflect a heightened vulnerability to PTSS/PTSD or alternatively, the expression of certain PTSS symptom dimensions. To our knowledge, only one study to date, conducted by our team, has used MRI techniques to examine the neurobiological correlates of cancer-related PTSS in children [9]. Understanding the developmental mechanisms linking pediatric cancer to the onset of PTSS/PTSD is essential to guide the development of evidence-based interventions to mitigate the effects of PTSS/PTSD and other psychosocial consequences of pediatric cancer throughout the lifespan.

This mini review examines neurobiological effects of pediatric cancer-related PTSS/PTSD by first considering the appropriateness of applying a trauma neurobiology framework to this population. Then, we briefly introduce the brain regions that are most relevant to PTSS/PTSD and review neuroimaging studies examining the structural and functional neural correlates of PTSS/PTSD in other pediatric populations. Next, we present a framework and the recommendations for future research in this area. In particular, concurrent evaluation of PTSS/PTSD and neuroimaging, as well as, consideration of sociodemographic, treatment-related, family factors and other stressors are needed to uncover mechanisms that explain the onset of PTSS/PTSD in some individuals following childhood cancer. We briefly review findings from neuroimaging studies on childhood cancer and one recent study on childhood cancer-related PTSS as a starting point in this endeavor.

Is cancer a potentially traumatic event for children?

The fact that childhood cancer is a stressful and potentially traumatic experience for children and their families is not surprising; families are faced with the news of a life-threatening disease and a 'new normal' that consists of frequent hospital visits and hospitalizations, painful and invasive treatments, health crises, physical limitations and side effects, and a disruption from normal aspects of day-to-day life. Stress does not end at the conclusion of treatment. There is persistent worry and fear over disease reoccurrence and children have to re-enter school after missing out on key educational and social experiences. Survivors must also learn to cope with new physical and mental limitations, including neurocognitive effects of treatment.

Table 1. Prevalence rates and predictors of posttraumatic stress disorder and symptoms in cancer and noncancer pediatric populations.

Factors	Childhood cancer populations	Noncancer populations	Ref.
Rates of PTSD	20–30%, although see [13,14]	8–15%	[8,11,33]
Characteristics of the disease/event	CNS tumors, more recent diagnosis, more comorbidity, physical late effects and disability	Severity of the event, injury severity, time post-trauma (negative association)	[34,35,36,37,38,39]
Characteristics of treatment	CNS-directed therapy, more intensive treatment, time since termination of treatment (negative association)	–	[30,40]
Characteristics of the child	Female gender, greater number of traumas/stressful life events, older age at diagnosis, nonwhite race, subjective appraisal of life threat and cancer-related beliefs	Female gender, IQ, greater number of traumas/stressful life events, acute stress reactions, nonwhite race, adaptive and maladaptive coping strategies, subjective appraisal of life threat, comorbid psychological problems	[4,18,20,34,38,39,41,42,43]
Characteristics of the family and environment	Poorer family functioning, lower social support, parenting style and parental distress, lower family income	Poorer family functioning, lower family and social support, parenting style and parent psychological problems, lower socioeconomic status	[4,39,44,45,46]

CNS: Central nervous system; PTSD: Posttraumatic stress disorder.

Nir [10] was the first to recognize that children respond to cancer and its treatment as they do to other life-threatening events. Since then, a wealth of research has applied a PTSS/PTSD framework toward understanding the experiences of children with cancer and psychosocial outcomes [11,12]. However, recent reports have called into question the appropriateness of a PTSD framework for understanding psychological consequences of pediatric cancer. This is driven by recent studies suggesting that rates of PTSD are similar in cancer and typically developing (i.e., noncancer) populations when using methods that minimize bias, for example, not referring to cancer as a trauma [13,14]. In fact, a large portion of patients and their families report that childhood cancer had a limited or even positive impact on their adjustment, such as posttraumatic growth and resilience [15]. In addition, almost half of children with cancer did not spontaneously report childhood cancer-related events to be their most traumatic or most stressful [13,16]. Rather, many children reported events that would not qualify as a potential trauma according to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) [17], such as death of a family member, parental divorce, and other family-related stressors. Even among noncancer populations, children frequently report bullying, death of a pet, or another event that wouldn't meet DSM-5 criteria for a trauma as their worst experience, despite also endorsing traumas such as physical assault or witnessing violence [18]. In tandem, the DSM-5, suggests that the diagnosis of a life-threatening illness such as cancer does not necessarily qualify as a traumatic event [17].

There is also literature to suggest that, among both cancer and noncancer pediatric populations, subjective perceptions of the event and the accumulation of both traumatic and stressful life events predict PTSS/PTSD [19–21]. These data highlight the importance of gathering a thorough history of stressful life events among childhood cancer populations, regardless of whether the events are potentially traumatic and cancer-related. They also indicate important individual differences in children's response to stress and trauma and highlight the difficulties centered around definitions of trauma and PTSD [22], which may be due, in part, to the fact that criteria were developed for adults and later adapted for children.

Table 1 shows a summary of rates and predictors of PTSS/PTSD in cancer and noncancer pediatric populations. One important factor for predicting PTSS/PTSD in children in particular is the proximal family system. Childhood cancer is a 'family disease' that requires all family members to adapt to recurring medical appointments, separation from family members and changing responsibilities, and worry over the health of the sick child. For some families, these stressors may disrupt family functioning by increasing family conflict or creating financial and marital stress [23,24]. Therefore, to understand a child's adjustment to a stressor and associated neurobiological effects, it is critical to consider the influence of family functioning and available resources. Indeed, previous research links higher anxiety and PTSS among survivors of childhood cancer and their parents to various family factors, including poorer family functioning and communication, higher conflict and less satisfaction within the family [25,26]. Family members – and parents in particular – may buffer the detrimental effects of cancer and its treatment on child adjust-

ment and associated neurobiological changes. Studies in both cancer and noncancer populations have reported that lower parental distress, higher social support, higher family resources, and a positive family environment (e.g., high expressiveness and cohesion, low conflict) are associated with less child distress [27–30]. There is also evidence that the quality of the parent–child relationship can improve adjustment among childhood cancer survivors [31]. Together, family and other environmental factors play a critical role in child adjustment to pediatric cancer and these factors should be included in research examining the underlying neurobiological correlates of pediatric cancer-related PTSS/PTSD. As one example, we demonstrated that the parent–child relationship modulated children's brain and behavioral responses to emotional conflict in a noncancer pediatric population [32]. These data suggest that the parent–child relationship and other proximal family factors can influence child adjustment by modifying the way that the developing nervous system interacts with emotionally charged information in the environment.

Although most children appear to cope psychologically well to childhood cancer and other potentially traumatic events, an emerging body of neuroscientific research suggests that the objective experience of a significant life threat induces structural and functional changes to the developing nervous system. These changes are apparent even in those who are psychologically well adjusted (for e.g., without a PTSD diagnosis) and may sensitize individuals and/or make them more vulnerable to subsequent stressors [47,48]. Therefore, for a child with cancer, the experience of a life-threatening disease and recurring painful treatments may alter neural development and leave them more susceptible to psychological problems after a relapse or recurrence of cancer or another negative event in childhood or adulthood. Thus, it is important to identify neurobiological changes that are induced by the event itself, as well as those related to the expression of PTSS/PTSD.

Structural & functional neural changes associated with childhood trauma

Neuroimaging studies suggest that a wide range of brain areas are affected by childhood trauma exposure (for a meta-analysis, see [49]). These areas span systems for basic sensory processes up to higher order cognitive and emotion-related functioning, which may explain the wide array of outcomes. Importantly, brain areas involved in threat detection, fear expression, and the ability to inhibit inappropriate fear responses are considered to be most relevant for PTSS/PTSD and other emotion-related outcomes [50]. Compared with the wealth of neuroimaging studies on PTSS/PTSD in adults, there are a limited number of studies in children with PTSS/PTSD. The existing pediatric studies show that many structural and functional changes in fear circuitry are similar to those reported in studies in adults, but some are unique to children (see meta-analysis by [51]). Differences are likely due to ongoing neurodevelopment in fear circuitry and preclude extrapolation of research findings from adult PTSD to the pediatric PTSS/PTSD literature.

Abnormalities in fear neural circuitry in pediatric posttraumatic stress symptoms/disorder and in pediatric cancer populations

The neural circuitry for fear is centered on four key areas (Figure 1): (1) the amygdala, involved in the detection of threat and expression of conditioned fear responding; (2) the ventromedial prefrontal and adjacent ventral anterior cingulate cortex (vmPFC/vACC), which play a key role in the extinction of fear responses via inhibitory control over amygdala responding; (3) the hippocampus, which is involved in contextual processing and can limit fear responses via direct and indirect connections to the amygdala via the vmPFC/vACC, and (4) the dorsal anterior cingulate cortex (dACC), which is implicated in the expression of learned fear.

Studies in adults consistently report hyperactivity of the amygdala, particularly in response to negative stimuli, in individuals with PTSS/PTSD relative to healthy controls [52,53]. Similar patterns have been reported in trauma-exposed youth and in adults with histories of childhood trauma exposure, even in the absence of PTSS/PTSD [54–56]. These data suggest that trauma exposure during development alters the tuning of the amygdala to emotionally charged information in the environment. Given the central role of the amygdala in orchestrating fear responses and in creating fear memories [57], hyperactivity of the amygdala may reflect a latent susceptibility to the development of PTSS/PTSD. Indeed, altered amygdala response may be the start of the developmental cascade that may disrupt other brain processes and regions, leading to the manifestation of PTSS (e.g., re-experiencing). In addition, childhood trauma-related changes in amygdala functionality that are evident even decades later into adulthood [e.g., 56] may explain why childhood trauma exposure is a potent risk factor for the emergence of PTSS/PTSD in both childhood and adulthood [58,59].

Importantly, only one study to-date has used MRI techniques to examine the neurobiological correlates of cancer-related PTSS in children [9]. This study focused on amygdala-based functional connections, given the central role

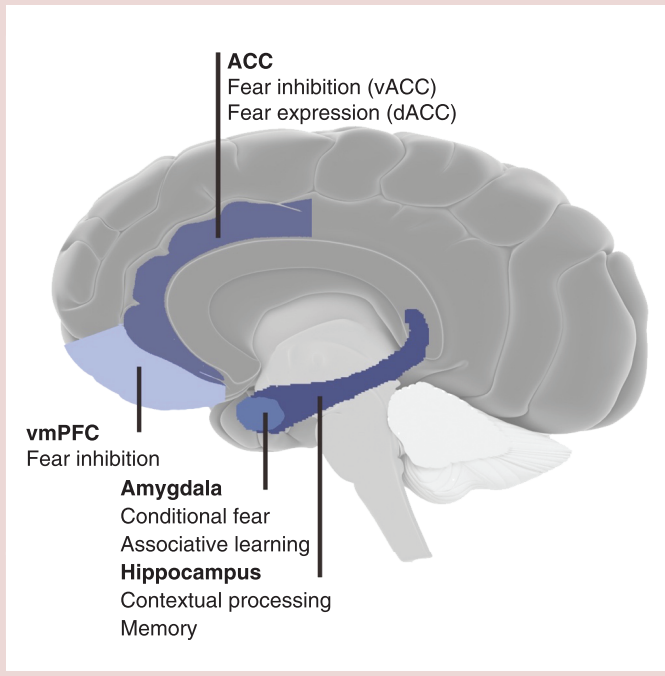

Figure 1. Summary of key regions in fear neural circuitry and their functions.
ACC: Anterior cingulate cortex; dACC: Dorsal anterior cingulate cortex; vACC: Ventral anterior cingulate cortex; vmPFC: Ventromedial prefrontal cortex.

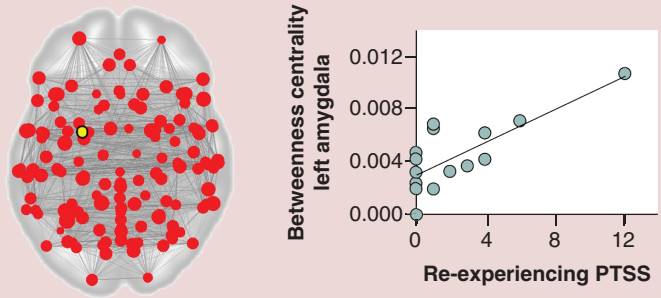

Figure 2. Childhood cancer survivors reporting higher re-experiencing posttraumatic stress symptoms show higher centrality of the amygdala, a measure that may reflect greater importance of this central fear region in terms of whole brain network functioning. Left: position of the left amygdala (yellow) in the whole-brain functional network. Size of the circle corresponds to betweenness centrality, which reflects the relative importance of that brain region to whole brain information processing. Right: positive correlation between re-experiencing PTSS and betweenness centrality of the amygdala in childhood cancer survivors.
PTSS: Post-traumatic stress symptom.
Adapted with permission from [9].

of this region in orchestrating the fear response and in fear-related learning [60]. Results show that childhood cancer survivors with higher cancer-related PTSS demonstrate increased centrality of the amygdala (Figure 2), a functional indicator of the relative importance of this region derived from resting-state functional connectivity (FC) measures. This effect was specific to re-experiencing PTSS, suggesting that fear networks involving the amygdala play a more prominent role in survivors who report more PTSS relative to survivors reporting lower PTSS. Examining

neurobiological correlates of specific PTSS dimensions will provide new insights into mechanisms leading to the development of pathology.

Another pattern that has been observed in trauma-exposed youth with and without PTSS/PTSD as compared with their healthy, unexposed counterparts is altered functional connectivity between the amygdala and the vmPFC/vACC [55,61–64]. The vmPFC/vACC is involved in automatic forms of emotion regulation, such as fear extinction, via top-down inhibitory control of amygdala reactivity [65]. Alterations in amygdala vmPFC/vACC functional connectivity have been reported in adults with PTSD relative to trauma-exposed controls without PTSD [66], and in trauma-exposed youth relative to their unexposed counterparts during an emotion regulation task as well as during a resting-state (i.e., outside of an explicit task [63,67]). Exposure to potentially traumatic events, such as childhood cancer, may induce abnormalities in a critical emotion regulatory pathway that mirror patterns observed in individuals with PTSS/PTSD. Thus, early developmental aberrations in amygdala vmPFC/vACC emotion regulation circuitry may predispose youth to the development of emotional psychopathology. However, no studies to-date have examined the impact of childhood cancer on behavioral measures of emotion regulation ability or underlying brain circuitry. Future studies should examine neural and behavioral measures of emotion regulation in childhood cancer survivors, that may help to explain why a subset of patients and survivors develop PTSS/PTSD.

Similar to studies in adults, lower volume of the vmPFC/vACC has been reported in youth with PTSS/PTSD as compared with healthy controls [68–70]. Consistent with these data, lower vmPFC volumes correlate with greater PTSS and longer illness duration [70]. However, volumetric reductions are not evident in trauma-exposed youth without PTSD relative to their unexposed counterparts, suggesting that lower vmPFC/vACC volume is an acquired trait that reflects the development of symptomology in vulnerable individuals rather than effects of the exposure itself. This idea is similarly supported in the adult PTSD literature [71]. Neuroimaging studies link lower volume of the vmPFC in youth with PTSD to higher re-experiencing PTSS, in particular [70]. This finding fits with data linking impairments in fear extinction with re-experiencing PTSS in particular [72], and the critical role of the vmPFC in extinction [60]. Although lower indicators of white matter integrity have been reported in medial frontal regions in childhood cancer survivors relative to controls [73], to our knowledge no studies have examined grey matter volume of the vmPFC, or correlations with cancer-related PTSS, in this population.

Smaller hippocampal volume has been consistently reported in adults with PTSD relative to healthy controls, including PTSD secondary to childhood trauma [74,75]. In children and adolescents, however, hippocampal volumes do not appear to differ in youth with PTSS/PTSD as compared with healthy controls. Rather, fitting with the chronic nature of stress exposure, previous research documents age-related decreases in hippocampal volumes in youth with PTSD, but not in healthy controls [70]. Alterations in the developmental trajectory of the hippocampus may contribute to delayed effects that reflect a latent vulnerability to psychopathology. Reductions in hippocampal volume over time are thought to be due to the detrimental effects of chronic glucocorticoid dysfunction and excess inflammation, which may result in reduced neurogenesis, dendritic atrophy, and/or neurotoxicity [76]. The high density of glucocorticoid receptors, particularly during development, together with the ongoing neurogenesis and maturation of this region, might make the hippocampus particularly sensitive to stress or other neurotoxic insults in early life [77]. Importantly, smaller hippocampal volumes are consistently reported in childhood cancer survivors relative to healthy controls, and these effects have been shown to scale with treatment intensity [78]. These effects are consistent with preclinical studies showing that the hippocampus is particularly sensitive to neurotoxic effects of chemotherapy and radiation [79]. However, no neuroimaging studies have examined the impact of PTSS on hippocampal volumes, or volume of other brain regions, in childhood cancer survivors. Given that more intense treatments are expected to correspond with greater PTSS/PTSD, longitudinal studies will be critical to track changes over time and include healthy siblings who are at a similarly elevated risk of PTSS/PTSD as patients but are not exposed to neurotoxic treatments.

Hyperactivity of the dACC has been reported in youth with PTSS/PTSD relative to healthy youth [80,81], and in childhood cancer survivors relative to healthy youth [82,83]. The dACC is implicated in threat appraisal and the expression of learned fear [65]. Both adults and youths with PTSD show a hyperresponse of this region to threat-related cues, which may contribute to PTSS via an exaggerated fear response [53,81]. Beyond fear, the dACC is implicated in a range of higher-order cognitive and emotion-related processes, including response inhibition, conflict resolution, and attentional control [84]. Carrion *et al.* [80] reported higher dACC response during a behavioral inhibition task in youth with PTSD relative to healthy controls. Interestingly, there were no differences in behavioral measures (accuracy, reaction time) between groups, suggesting that youth with PTSD had to engage a higher level of

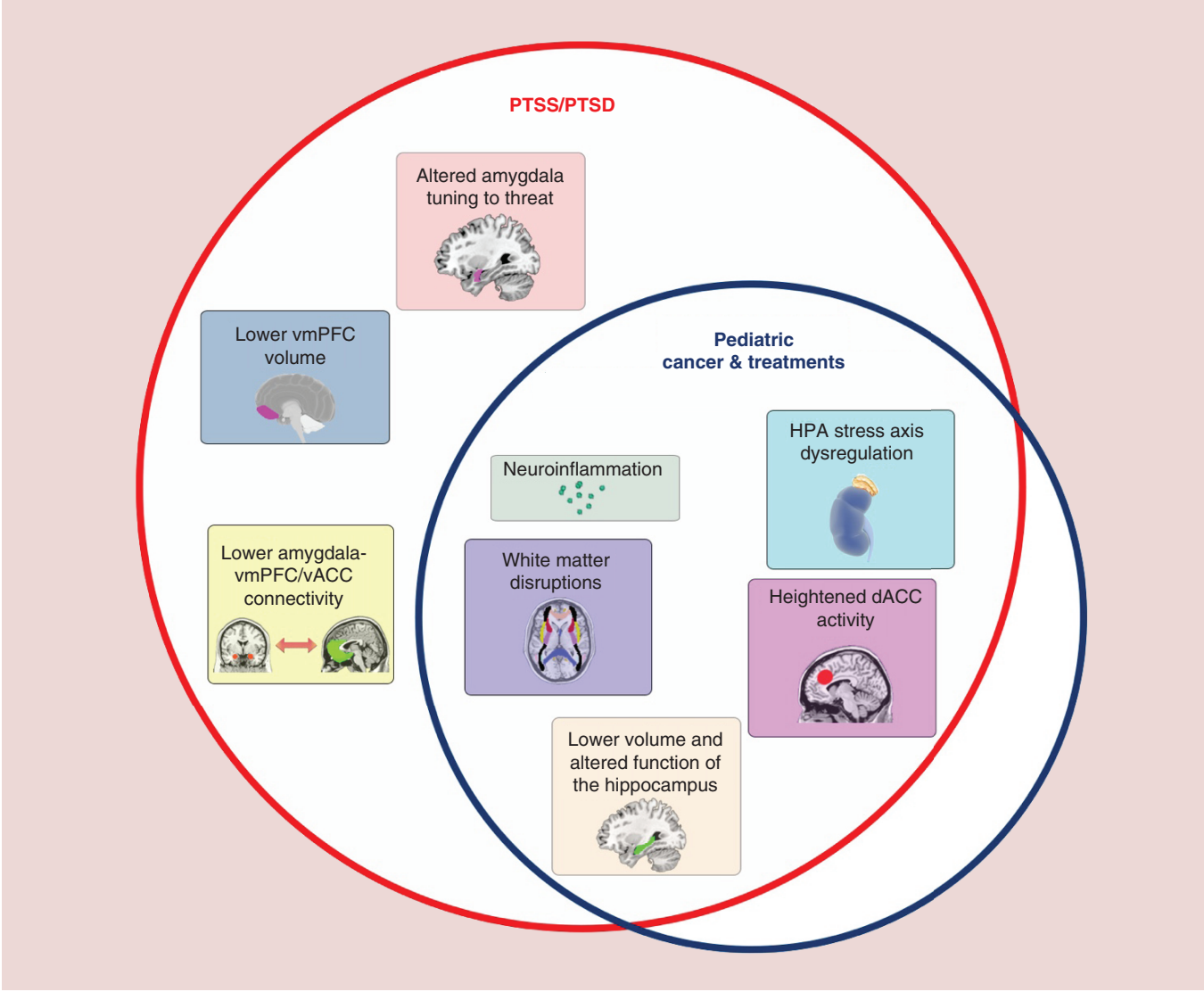

Figure 3. Neurobiological changes associated with childhood trauma exposure and/or pediatric PTSD and symptoms, and overlapping patterns observed in childhood cancer survivors. See Table 2 for a summary of specific structural and functional changes associated with pediatric PTSS/PTSD, and those reported in childhood cancer survivors. Of note, there are patterns observed for pediatric PTSS/PTSD that have not yet been explored in pediatric cancer populations.
dACC: Dorsal anterior cingulate cortex; HPA: Hypothalamic pituitary adrenal: PTSD: Posttraumatic stress disorder; PTSS: Posttraumatic stress symptom; vACC: Ventral anterior cingulate cortex; vmPFC: Ventromedial prefrontal cortex.

dACC activity to maintain the same level of performance. Strikingly similar patterns have been observed in young leukemia survivors, such that survivors showed higher dACC response during an attentional control task relative to healthy controls, yet there were no group differences in behavioral performance [82]. This neurobehavioral pattern is thought to reflect over-engagement of higher-order regulatory control regions among survivors to compensate for damage in other brain areas. Together, these findings suggest aberrant engagement of the dACC that may reflect a compensatory mechanism to regulate cognitive and emotion-related processing in the context of neurotoxic effects of cancer treatments and/or traumatic stress.

Figure 3 shows neurobiological changes associated with exposure to childhood trauma and pediatric PTSS/PTSD, and the overlapping patterns observed in childhood cancer populations that may be related to pediatric cancer and/or its treatment. Importantly, there are patterns observed for pediatric PTSS/PTSD that have not yet been explored in pediatric cancer populations. Structural or functional factors in the basic neural circuitry involved in fear-related processing may be critical for the development of PTSS/PTSD in pediatric cancer populations.

Table 2. Summary of neuroimaging findings in fear circuitry in pediatric posttraumatic stress disorder and symptoms and trauma exposure, and in pediatric oncology populations.

Brain region	Childhood cancer	Childhood trauma and/or pediatric PTSS/PTSD	Ref.
Hippocampus	Lower hippocampal volume among survivors relative to controls Lower hippocampal activation during memory retrieval among adult survivors of childhood cancer Increased white matter nodal clustering of the hippocampus among survivors relative to controls Lower rs-FC of the hippocampus with several brain regions involved in attention and visual processing in survivors relative to controls	Age-related decrease in hippocampal volumes in pediatric PTSD vs healthy youth, and lower hippocampal volumes among adults with histories of childhood trauma exposure vs. without Lower hippocampal activation during memory retrieval among youth with PTSS relative to controls Higher centrality of the hippocampus among youth with PTSD relative to controls, as measured using rs-FC and gray matter volumes	[70,85–96]
dACC	Higher activation in the anterior cingulate cortex during a working memory task in youth with cancer in comparison to controls Lower normal-appearing white matter volume in the anterior cingulate in comparison to controls Lower anterior cingulate activation during an attention task with higher prior methotrexate exposure among survivors, ages 10–17 years	Higher dACC response during a behavioral inhibition task in youth with interpersonal trauma-related PTSS, and during a threat processing paradigm in youth with PTSD relative to controls Lower resting-state functional connectivity of the anterior cingulate cortex with the salience and emotion network in youth exposed to interpersonal trauma relative to controls Lower dACC volume among youth with sexual abuse-related PTSD	[80–83,97–100]
vmPFC/vACC	Lower indicators of white matter integrity in medial frontal regions among survivors relative to controls	Lower vmPFC volume in youth with PTSD relative to either controls, or trauma-exposed youth without PTSD (although see [94]) Longitudinal decrease in vmPFC-amygdala rs-FC among youth with PTSD, and lower vmPFC-amygdala functional connectivity during threat processing	[68,69,73,81]
Amygdala	Lower rs-FC of the amygdala with attention and visual processing regions among survivors relative to controls Lower gray matter volume of the amygdala in survivors relative to controls Lower white matter clustering of the amygdala in survivors relative to controls Greater re-experiencing PTSS associated with higher centrality of the amygdala among childhood cancer survivors	Increased amygdala response, particularly to negative stimuli, is associated with childhood trauma exposure Youth with PTSD show age-related increases in amygdala response to threatLower volume of the amygdala among adults with histories of childhood trauma Less negative functional connectivity between the amygdala and vmPFC/vACC among youth with trauma exposure and/or PTSD relative to controls	[9,55,56,61,70,86,91,92,101–108]

dACC: Dorsal anterior cingulate cortex; PTSD: Posttraumatic stress disorder; PTSSS: Posttraumatic stress symptoms; rs-FC: Resting-state functional connectivity; vACC: Ventral anterior cingulate cortex; vmPFC: Ventromedial prefrontal cortex.

Future perspective

Together, it is clear that most children with cancer cope psychologically well following these experiences. This is reflected in relatively low rates of PTSD. However, a significant subset will experience PTSS/PTSD, which has critical implications for medical and psychological outcomes for children and their families. A growing body of neuroimaging research indicates that exposure to childhood trauma, even in the absence of PTSS/PTSD or other psychological problems, fundamentally alters neurodevelopment. Neurobiological changes, particularly in regions of the fear neural circuitry, may represent a latent susceptibility to the development of PTSS/PTSD years or even decades later. Although several neuroimaging studies in pediatric cancer survivors document structural and functional neural changes that mirror those reported on childhood trauma and/or pediatric PTSS/PTSD (Table 2), only one study to date has linked PTSS to brain changes in childhood cancer survivors. The limited research on the neural correlates of pediatric cancer-related PTSS is in stark contrast to the well documented psychosocial impacts of pediatric cancer. Future studies that measure PTSS/PTSD as well as neural changes in childhood cancer populations are needed to identify mechanisms underlying the development of PTSS/PTSD in this population. As we see from studies on childhood trauma and PTSS/PTSD, neural changes may be associated with children's response to stress and trauma and are thus induced by the experience itself (even in the absence of PTSS/PTSD), whereas other neural changes may track the expression of specific PTSS dimensions (e.g., re-experiencing). Specific brain areas may be sensitive to neurotoxic effects of treatment and interact with traumatic stress during development (e.g., hippocampus). Future studies should aim to disentangle effects of the exposure from symptomology by comparing three groups – healthy controls, those with cancer and PTSS/PTSD and

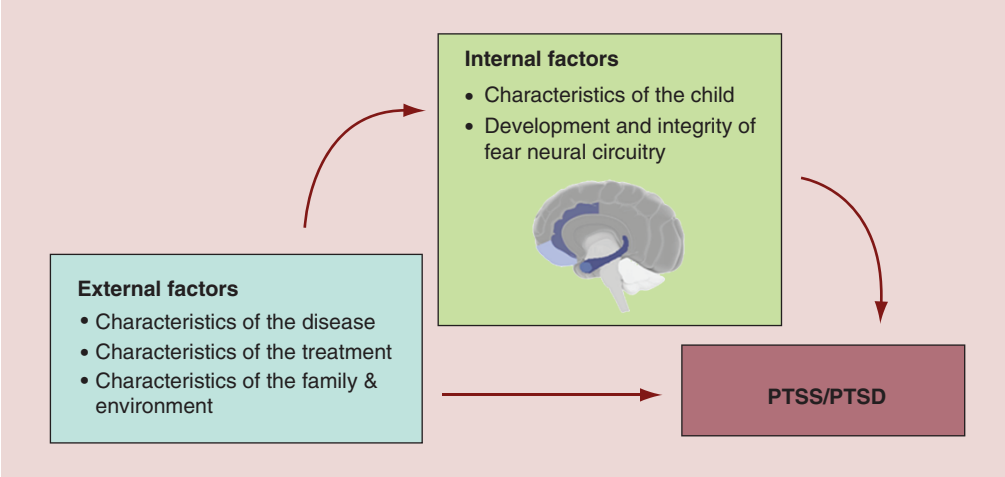

Figure 4. Development or integrity of fear neural circuitry may mediate the association between external risk factors (e.g., poor family functioning) and pediatric cancer-related pediatric posttraumatic stress disorder and symptoms. See Table 1 for summary of reported predictors of cancer-related PTSS/PTSD in pediatric oncology populations.
PTSD: Posttraumatic stress disorder; PTSS: Posttraumatic stress symptom.

survivors without PTSS/PTSD – or examine severity of PTSS as a continuous measure. Additional focus should be given to identifying compensatory neural mechanisms that protect against the development of psychopathology that may be evident in exposed individuals without PTSS/PTSD. Several characteristics of the child, family, disease and treatments have been shown to predict PTSS/PTSD among children with cancer, including female gender, CNS-directed therapy, perceived life threat and the accumulation of other stressful or traumatic life events (Table 1). These factors may similarly be associated with changes in fear neural circuitry that lead to the expression of PTSS/PTSD, as demonstrated in Figure 4. For example, the presence of family and social support buffers may be stronger among childhood cancer survivors than those exposed to other forms of trauma (e.g., sexual abuse) which may be more isolating and contribute to higher rates of PTSS/PTSD in these populations. Concurrent evaluation of PTSS and neuroimaging outcomes, as well as consideration of sociodemographic, treatment-related or family factors and other stressors, is needed to uncover mechanisms that explain the onset of PTSS/PTSD in some individuals following childhood cancer.

The high rates of cancer-related PTSS highlight the need for screening of youth for PTSS/PTSD and other clinical symptomology and subsequent referral to psychosocial care, during and after their treatments for cancer. Neuroimaging research on biological markers of cancer-related PTSS is needed to advance psychosocial models that explain individual differences in psychological outcomes and health consequences among pediatric patients and survivors. Neuroimaging research may also inform clinical practice by guiding the development of evidence-based interventions that target underlying mechanisms leading to cancer-related PTSS/PTSD. For example, recent studies in adults with PTSD have incorporated neuroimaging and report that successful PTSD treatment (via cognitive-behavioral therapy) can modulate activity in limbic regions implicated in fear and PTSD/PTSS, including the amygdala, hippocampus, and dACC [109]. Evidence that interventions can modulate fear neural circuitry also strengthens empirical evidence of treatment efficacy and may help to optimize mental health outcomes in pediatric cancer patients and survivors.

Financial & competing interests disclosure

HA Marusak is supported by American Cancer Society award 129368-PF-16-057-01-PCSM. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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