

Smaller Hippocampal Volume Is Associated With Reduced Posttraumatic Stress Symptoms in Children With Cancer and Survivors Following a Brief Novel Martial Arts-Based Intervention

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Abstract

Purpose: Children with cancer and survivors frequently report posttraumatic stress symptoms (PTSS), which are associated with volumetric changes in stress-sensitive brain regions, including the hippocampus.

Methods: We examined the impact of a novel, 4-week martial-arts-based meditative intervention on cancer-related PTSS in 18 pediatric patients and survivors and whether baseline hippocampal volumes correlate with PTSS severity and/or PTSS changes over time.

Results: Overall, PTSS did not significantly change from baseline to post-intervention. Smaller hippocampal volume was correlated with more severe re-experiencing PTSS at baseline, and greater reductions in PTSS post-intervention.

Conclusions: Together, hippocampal volume may be a biomarker of PTSS severity and intervention response. Identifying hippocampal volume as a potential biomarker for PTSS severity and intervention response may allow for more informed psychosocial treatments.

Keywords: Neuroimaging; Children; Adolescents; Psycho-oncology; Mindfulness; Posttraumatic stress disorder

Introduction

Pediatric cancer rates have increased over the past four decades; in 2022, an estimated 15,950 U.S. youth were diagnosed with cancer (ACS, 2021). Fortunately, treatment advances have increased survival rates, with 85% of children surviving at least five years after diagnosis (ACS, 2021). Children with cancer, survivors, and their family members report significant psychosocial stress related to fear of dying, long hospital stays, medical procedures, and loss of control (McCaffrey, 2006). Further, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5; American Psychiatric Association, 2013), childhood cancer can be a traumatic event severe enough to fulfill the requirements of a Criterion A1 trauma exposure

(see Bruce, 2006). Indeed, the diagnosis of cancer itself represents a significant threat to life, which is a core component of traumatic stress. Further, the multiple experiences of invasive treatment procedures, intensive care, or learning that other children have died may evoke intense fear or helplessness, or other trauma-related symptomatology (Center for Substance Abuse Treatment, 2014).

While full-spectrum posttraumatic stress disorder (PTSD) may be more rare (Kosir et al., 2019), an alarming up to 82% of youth with cancer or survivors report posttraumatic stress symptoms (PTSS), such as involuntary recurrent memories or nightmares, emotional numbing, and heightened physiological arousal (Krull et al., 2013; Marusak et al., 2019a; Oancea et al., 2014). The four main subtypes of PTSS are re-experiencing (e.g., nightmares, flashbacks, intrusive thoughts), negative affect (e.g., persistent negative emotional state, diminished interest or participation in significant activities), hyperarousal (e.g., hypervigilance, sleep disturbances), and avoidance (e.g., isolating oneself from external or internal reminders about the event). Prior studies suggest that re-experiencing and hyperarousal PTSS may be more common than other subtypes among pediatric cancer populations (Kazak et al., 2001; Stewart et al., 2020).

Cancer-related PTSS have been associated with functional and structural alterations in the developing brain, particularly in fear-related neurocircuitry (Marusak et al., 2019a; Marusak et al., 2019b). For example, we have previously demonstrated that children with more cancer-related PTSS—particularly re-experiencing PTSS—demonstrate larger volumes of the right amygdala, a brain region involved in mediating fear and stress responses and shown to be sensitive to early adversity (Stewart et al., 2020). PTSS is also predictive of later behavioral problems (e.g., poor social competence, internalizing or externalizing problem behaviors) in survivors of childhood cancer (Barakat et al., 2000). The high prevalence of PTSS and associated neurodevelopmental changes underscores the need to improve psychosocial outcomes among pediatric cancer populations.

Emerging data indicate that mindfulness, breathing, and meditation practices are promising for relieving pain and emotional distress in pediatric cancer populations (Stritter et al., 2021; Wang et al., 2022). We have previously demonstrated that a 60-min mindfulness-oriented martial-arts therapy (MAT) session is associated with reductions in these symptoms in children with cancer and survivors (Bluth et al., 2016; Marusak et al., 2020). Some of this work has been done in collaboration with Kids Kicking Cancer (KKC; <https://heroescircle.org/>), a non-profit MAT that incorporates meditation, breathing exercises, and empowering movements to help children learn to cope with pain and distress associated with the disease and/or treatments. KKC is now in 10 countries and 21 U.S. states and provides these services to children with cancer, sickle cell, other chronic illnesses, and their siblings as a part of the “Heroes Circle.” The mantra of KKC is “Power. Peace. Purpose.” which emphasizes feelings of empowerment and self-regulation. In collaboration with KCC, we have shown that MAT is effective for lowering pain and emotional distress (i.e., “how unpleasant or bad you feel”) in other populations, including children with sickle cell, schoolchildren, and adults with opioid use disorder (Faraj et al., 2021; Marusak et al., 2020, 2022).

Recent research has demonstrated that mindfulness training is associated with functional changes in stress-sensitive brain regions, including the hippocampus (Sevinc et al., 2019), which is involved in stress regulation, learning, and emotional memory. The hippocampus is also thought to be susceptible to PTSS (Del Casale et al., 2022). In particular, lower volume of the left hippocampus is frequently associated with more severe PTSS (Logue et al., 2018; Nelson & Tumpap, 2017) and predicts PTSD development over time (Xie et al., 2018). Moreover, smaller hippocampal volumes at baseline have been related to greater reductions in PTSS in adults following an intervention (Suarez-Jimenez et al., 2020). Thus, hippocampal volume may serve as a biomarker of pathology and of future intervention response. Of note, biomarkers of PTSS or treatment response are correlative rather than causal, and that there are both environmental and genetic contributions to risk of developing PTSS (Michopoulos et al., 2016; Pacella et al., 2013).

Although MAT has been shown to acutely reduce emotional distress in children with cancer and survivors (Marusak et al., 2020), less is known about effects following multiple sessions on PTSS. Further, while studies in adults suggest that hippocampal volume may be a biomarker of PTSS severity and of intervention response, no studies have examined these neurobiological correlates in pediatric cancer populations. Our pilot study aimed to examine the effects of a four-week MAT on cancer-related PTSS in children with cancer and survivors. Baseline neuroimaging scans were performed to evaluate whether hippocampal volumes were associated with baseline PTSS or change in PTSS from baseline to post-intervention.

Materials and Methods

Participants

Eighteen children with cancer or survivors participated in this 4-week prospective study (see Table 1). Participants were recruited from the Children’s Hospital of Michigan, KKC, and local cancer support groups (e.g., Gilda’s Club). Participants were eligible if they were between the ages of 5 and 17 years upon enrollment, provided assent and had a parent/legal guardian provide consent and attend study sessions, had a lifetime diagnosis of pediatric cancer that did not include the central nervous system

Table 1. Participant demographics and clinical information

Variable	<i>n</i> (%)	<i>M</i> (<i>SD</i>)	Range
Age upon enrollment (years)		10.7 (2.97)	5–17
Age at diagnosis (years)		5.6 (4.07)	1–17
Time since diagnosis (years)		5.1 (2.76)	0.75–9
Biological sex (females)	8 (44%)		
Treatment status			
Current treatment (patient)	5 (27.8%)		
Past treatment (survivor)	13 (72.2%)		
Cancer diagnosis			
Acute lymphoblastic leukemia (ALL)	12 (66.4%)		
Acute promyelocytic leukemia (APML)	1 (5.6%)		
B-cell lymphoma	1 (5.6%)		
Neuroblastoma	1 (5.6%)		
Wilms tumor	1 (5.6%)		
Ewing's sarcoma	1 (5.6%)		
Juvenile myelomonocytic leukemia (JMML)	1 (5.6%)		
Race/ethnicity			
White, Non-Hispanic	10 (55.5%)		
White, Hispanic	1 (5.6%)		
Black, Non-Hispanic	4 (22.2%)		
Other	2 (11.1%)		
Not reported	1 (5.6%)		
Annual household income			
\$0–9,999	1 (5.6%)		
\$10,000–19,999	1 (5.6%)		
\$20,000–29,999	2 (11.1%)		
\$30,000–39,999	3 (16.6%)		
\$40,000–49,000	3 (16.6%)		
\$50,000–59,000	0 (0%)		
\$60,000–79,999	3 (16.6%)		
\$80,000–99,999	1 (5.6%)		
\$100,000–119,999	2 (11.1%)		
\$120,000–140,000	1 (5.6%)		
Not reported	1 (5.6%)		
Baseline PTSS		17.37 (14.56)	3–64
Re-experiencing PTSSs		4.22 (4.89)	0–19
Avoidance PTSS		2.11 (2.52)	0–7
Negative affect PTSSs		4.11 (5.13)	0–22
Hyperarousal PTSS		5 (4.22)	0–16

Note: PTSS were assessed using the adolescent self-report UCLA PTSD Reaction Index for DSM-5 (Doric et al., 2019). PTSS: posttraumatic stress symptoms.

(measured via parent/guardian and/or clinician report), and were free of magnetic resonance imaging (MRI) contraindications. The Wayne State University Institutional Review Board approved the study protocol.

Overall Study Design

Participants were interviewed by trained members of the research staff (i.e., clinical psychology doctoral students or a postdoctoral research fellow) about their cancer-related PTSS and underwent MRI at baseline. Participants then completed four, 60-min in-person KKC classes. The 4-week intervention was selected to limit participant burden and enhance feasibility of this preliminary study. The PTSS were reassessed following the completion of the four classes (Fig. 1a).

Martial Arts Therapy

KKC classes are led by specially trained black belt-level martial arts therapists following a Choi Kwang Do-based curriculum developed by Rabbi Elimelech Goldberg, a black belt and founder of KKC. KKC classes typically include a mix of children with cancer, other chronic health conditions, and siblings, which allows for a unique platform to share similar experiences and how MAT techniques can be used to overcome daily challenges. KKC classes typically begin with recitation of the mantra “Power.

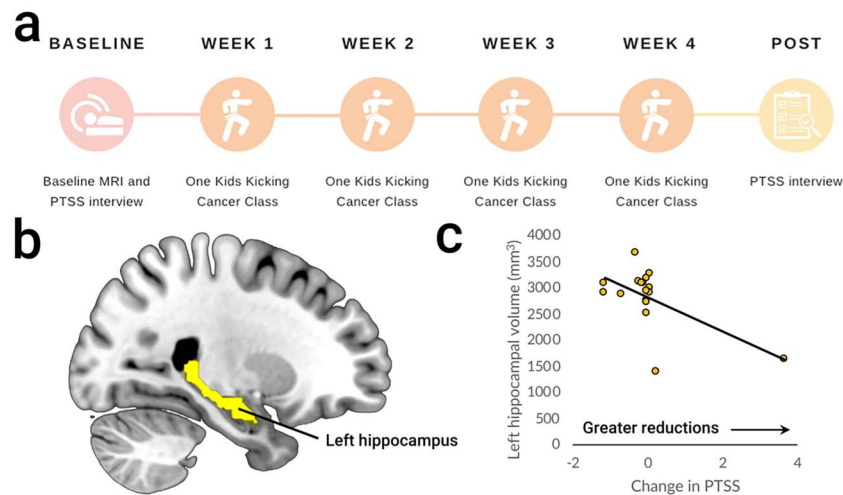


Fig. 1. Study timeline (a) left hippocampus (b) and association between baseline hippocampal volume and change in posttraumatic stress symptoms (c).

Peace. Purpose.,” followed by deep breathing exercises, an introspective body scan, instruction of specific techniques (e.g., “Ninja Needle” technique for needle-related procedures), and a series of non-contact moving meditations (e.g., kicks, punches). For more information about KKC classes and techniques, please see [Marusak and coworkers \(2020\)](#) and [Bluth and coworkers \(2016\)](#). Martial arts therapists are also embedded in clinics to provide bedside support and interventions in the hospital setting.

Cancer-Related PTSS

PTSS were measured using the UCLA PTSD Reaction Index for DSM-5 ([Doric et al., 2019](#); [Kaplow et al., 2020](#)), a 31-item measure that was created and validated for children and adolescents up to age 25 ([Allwood, 2020](#)). The UCLA PTSD Reaction Index demonstrated excellent validity in a study of over 4,000 adolescents from 11 countries worldwide (Cronbach’s $\alpha = .92$; [Doric et al., 2019](#)), and consists of the four PTSS subtypes: re-experiencing (5 items; possible range: 0–20), avoidance (2 items; possible range: 0–8), negative affect (7 items; possible range: 0–28), and hyperarousal (6 items; possible range: 0–24). We have previously applied this measure to examine cancer-related PTSS in youth ([Marusak et al., 2018](#); [Stewart et al., 2020](#)). We computed an overall PTSS severity score (possible range: 0–80) at baseline and post-intervention. Then, change scores were computed to indicate within-subject response to intervention, that is, PTSS at baseline minus post-intervention, such that higher scores indicate greater reductions in PTSS over time. The PTSS subtypes (i.e., re-experiencing, avoidance, negative affect, hyperarousal) were also examined.

Neuroimaging Data Acquisition

Neuroimaging data were collected using a research-dedicated 3 T MRI scanner (Siemens MAGNETOM Verio) at the Wayne State University MR Research Facility, using a 32-channel head coil. T1-weighted anatomical images were captured using a magnetization-prepared gradient-echo (MP-RAGE) sequence: repetition time = 1,680 ms, echo time = 3.51 ms, flip angle = 9 degrees, base resolution = 384, FOV = 256×256 , voxel size = $0.7 \times 0.7 \times 1.34$ mm³, 128 slices.

Gray Matter Volume Analysis

MRI data were processed following our prior work ([Stewart et al., 2020](#)), using the automated cortical and subcortical extraction pipeline within BrainSuite software (v.18a) ([Shattuck & Leahy, 2002](#)). Following visual inspection, total volume (gray matter and white matter) of the left and right hippocampus (mm³) were estimated. Total intracranial volume (i.e., gray matter, white matter, and cerebrospinal fluid) was estimated for use as a covariate.

Statistical Analyses

To test our first aim, Related-Samples Wilcoxon Signed Rank Test was used to examine within-subjects significant changes in PTSS over time (baseline vs. follow-up). Then, regressions were used to examine whether baseline hippocampal volumes

were associated with baseline PTSS or PTSS change scores, adjusting for total intracranial volume. Overall PTSS and subtypes were examined. Follow-up analyses were conducted to test for specificity of results to gray matter versus white matter. All analyses were performed in SPSS v.27.0 (IBM Corp, 2020) at $p < .05$ (two-tailed). Age, gender, and race did not show significant bivariate associations with PTSS, change in PTSS, or hippocampal volumes ($p > .1$). Therefore, to preserve statistical power, we did not include these or other variables as covariates. PTSS and hippocampal volumes were screened for outliers ($|Z| > 3$) and for violations of univariate assumptions. Three participants were missing post-intervention PTSS scores; therefore, mean imputation was used (Sinharay et al., 2001). Descriptive statistics were used to characterize baseline PTSS and change scores. There were no outliers in PTSS. However, change scores were not normally distributed (Shapiro–Wilk test $p = .03$); thus, non-parametric tests were applied. There were no outliers in hippocampal volumes. After adjusting for total intracranial volume, hippocampal volumes were normally distributed (Shapiro–Wilk test $p > .2$).

Results

Eighty-nine percent of youth reported PTSS (i.e., severity scores > 0) at baseline. Hyperarousal was the most prevalent subtype, followed by re-experiencing, negative affect, and avoidance (see Table 1). There were no significant differences in overall PTSS ($Z = 1.02$, $p = .31$) or subtypes ($ps > .1$) from baseline to post-intervention. At baseline, overall PTSS were not significantly associated with volume of the left or right hippocampus. However, smaller left ($F(2, 17) = 6.54$, $p = .009$, $\beta = -0.77$, $p = .004$) and right ($F(2, 17) = 4$, $p = .041$, $\beta = -0.65$, $p = .019$) hippocampal volumes at baseline were associated with more severe re-experiencing PTSS. Further, smaller left hippocampal volumes at baseline were associated with greater reductions in PTSS from baseline to post-intervention ($F(2, 17) = 4.41$, $p = .031$, $\beta = -0.542$, $p = .041$; Fig. 1b and c). This association was specific to gray matter ($p = .014$) as compared to white matter volume ($p = .47$) and was driven by reductions in both re-experiencing ($p = .011$) and negative affect ($p = .046$) PTSS subtypes. Left hippocampal volume was not significantly associated with change in avoidance or hyperarousal PTSS subtypes ($ps > .5$). Right hippocampal volume was not significantly associated with PTSS change scores, $p = .067$.

Discussion

This study showed several notable results. First, there was no significant change in PTSS from baseline to post-MAT intervention in this sample of children with cancer and survivors. Next, smaller hippocampal volumes were associated with more severe trauma-related symptomatology at baseline, which is consistent with prior studies in adults (Logue et al., 2018; Nelson & Tumpap, 2017). Smaller hippocampal volume has been reported in adults (Bergouignan et al., 2011) and children (Monje et al., 2013) with cancer and survivors, suggesting sensitivity of the hippocampus to the neurotoxic effects of stress and/or cancer treatment (Marusak et al., 2018, 2019b).

Third, youth with smaller hippocampal volumes at baseline demonstrated greater reductions in cancer-related PTSS following a brief 4-week MAT. Interestingly, baseline hippocampal volume predicted reductions in re-experiencing and negative affect PTSS subtypes in particular, which is consistent with the notion that volumetric reductions of the hippocampus are associated with intrusive memories and mood/affect disruptions associated with PTSSs (cf. Del Casale et al., 2022). Re-experiencing PTSS is particularly prevalent in both adult and pediatric cancer populations (Marusak et al., 2019a). Prior research in breast cancer survivors linked greater re-experiencing PTSS to smaller hippocampal volumes (Hara et al., 2008), and we have previously linked re-experiencing PTSS to larger amygdala volume and altered centrality of the amygdala—suggesting greater functional importance—in pediatric cancer populations (Marusak et al., 2019a; Stewart et al., 2020). Null results for other PTSS subtypes may be related to the restricted range observed in our sample, particularly of avoidance PTSS. Together, hippocampal volumes may serve not only as a promising biomarker of symptom severity but also as a potential predictor of response to psychosocial intervention. Future iterations of this MAT may be adapted to address other PTSS subtypes, or MAT should be used in combination with other pharmacological or behavioral treatment approaches. For instance, prazosin is a central nervous system active alpha-1 adrenoreceptor blocker that may be effective for reducing hyperarousal symptoms in adults with PTSD (Raskind, 2015).

Interestingly, we found that the effects of baseline PTSS and change in PTSS following the MAT were specific to the left hippocampus. Prior meta-analyses of MRI studies have reported volumetric reductions in both left and right hippocampus in adults and children with PTSD relative to healthy controls (with or without trauma exposure; Kribakaran et al., 2021; Nelson & Tumpap, 2017). These findings suggest that smaller hippocampal volume may predispose some individuals to developing PTSD following a trauma (Gilbertson et al., 2002) and/or that PTSD and/or trauma exposure itself are neurotoxic to both left and right hippocampus. However, lower volume of the left (but not right) hippocampus has been associated with greater PTSS severity (Nelson & Tumpap, 2017) and is reported in adults with PTSD relative to trauma-exposed controls without PTSD

(Del Casale et al., 2022)—suggesting that PTSS may be neurotoxic to the left hippocampus, in particular. Conversely, a recent coordinate-based meta-analysis linked volumetric reductions in the *right* (but not left) hippocampus to early life adversity exposure in youth (Pollok et al., 2022). Together, these findings raise the intriguing possibility that the right hippocampus is more sensitive to early stress or trauma exposure, whereas the left is more sensitive to the expression of PTSS. It is unclear why left hippocampal volume may be more closely related to PTSS than right hippocampal volume, and future preclinical studies are needed to uncover the mechanistic causes and functional implications of these findings, for example, cortisol-induced dendritic atrophy (Sapolsky et al., 2013). This hemispheric asymmetry may also relate to the distribution of emotional processing in general, wherein *social* emotions and related behaviors are preferentially modulated by the left hemisphere of the brain (Ross, 2021).

The lack of significant change in overall PTSS or PTSS subtypes may be due to small sample size, heterogeneity in cancer diagnoses, treatments, relatively wide age range, sex, and race/ethnicity. To lessen the effects of age and other individual differences on our analyses, we focused on within-subject differences in PTSS over time, and hippocampal analyses were adjusted for total intracranial volume, which is standard practice for adjusting for head size (Voevodskaya et al., 2014). Similarly, to maximize sample size, we used mean imputation to account for missing data, which may have influenced our results—particularly if data are not missing at random (Sinharay et al., 2001). It is also possible that four sessions was not a sufficient duration and/or frequency to assess change, and eight or more weeks may be needed (Boyd et al., 2018). However, a recent study reported significant reductions in PTSS following a brief 4-week mindfulness intervention in a sample of veterans with PTSD (Possemato et al., 2022). Future studies might benefit from a longer intervention period, including a control group, a post-intervention measure of hippocampal volume, and a larger sample size to better assess the effects of MAT on PTSS. Prior studies have demonstrated that treatment protocol, length of treatment, chemotherapy dose and agent, age at diagnosis, and diagnosis can affect brain morphology as well as cancer-related PTSS (Marusak et al., 2018, 2019b). Therefore, future studies with larger sample sizes should examine the impact of these variables on hippocampal volumes and PTSS.

Results of this preliminary study suggest that smaller hippocampal volume is correlated with more severe cancer-related PTSS and greater response to a 4-week MAT in a pediatric cancer sample. This extends prior research on effects of MAT and mindfulness-based practices on mental health in youth. While prior studies consistently report lower hippocampal volume in individuals with non-cancer-related PTSD (Hara et al., 2008), more research is needed to examine this biomarker in pediatric cancer populations and explore associations among hippocampal volume, PTSS, and treatment response. Our findings contribute to a new understanding of the neural underpinnings of cancer-related PTSS in youth. They also highlight potential biomarkers that can be used to identify individuals at greatest need for intervention and guide more individualized psychosocial interventions. For instance, children with more re-experiencing PTSS and/or smaller hippocampal volumes at baseline may benefit most from MAT. Other complementary interventions may be needed to address other PTSS subtypes, such as hyperarousal.

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Conflict of Interest statement

EG is the Founder and Global Director and MB is the Global Medical Director of Kids Kicking Cancer. The authors have no other conflicts to disclose.

Data Availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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