Smaller hippocampal volume is associated with reduced posttraumatic stress symptoms in pediatric cancer patients and survivors following a brief novel martial arts-based intervention

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Abstract

Pediatric cancer patients and survivors frequently report posttraumatic stress symptoms (PTSS), which are associated with variation in stress-sensitive brain regions, including the hippocampus. We examined the impact of a novel, four-week martial-arts-based meditative intervention on cancer-related PTSS in pediatric patients and survivors, and whether hippocampal volumes at baseline correlate with PTSS severity and/or changes in PTSS over time. PTSS did not significantly change from baseline to post-intervention. However, smaller hippocampal volume was correlated with more severe re-experiencing PTSS at baseline, and greater reductions in PTSS post intervention. Together, hippocampal volume may be a biomarker of PTSS severity and intervention response.

Introduction

Pediatric cancer rates have increased over the past four decades; in 2022, an estimated 15,950 U.S. youth were diagnosed with cancer [1]. Fortunately, treatment advances have increased survival rates, with 85% of children surviving > 5 years after diagnosis [1]. The growing incidence and survival rates highlight the need to improve psychosocial outcomes among pediatric cancer populations.

Pediatric cancer patients, survivors, and their family members report significant psychosocial stress related to fear of dying, long hospital stays, medical procedures, and loss of control [2]. Alarmingly, up to 82% of young survivors report posttraumatic stress symptoms (PTSS), which often include involuntary recurrent memories or nightmares, emotional numbing, and heightened physiological arousal [3–5]. Cancer-related PTSS have been associated with functional and structural alterations in the developing brain, particularly in fear-related neurocircuitry [5,6], and predicting long-term adjustment [7].

Emerging data indicate that mindfulness, breathing, and meditation practices are promising for relieving pain and emotional distress in pediatric cancer populations [8,9]. Our group demonstrated that a 60-minute mindfulness-oriented martial-arts therapy (MAT) session is associated with reductions in these symptoms in children with cancer and survivors [10,11].

Recent research has demonstrated that mindfulness and MAT are associated with functional changes in stress-sensitive brain regions, including the hippocampus [12], which is involved in stress regulation, learning, emotional memory, and susceptibility to PTSS. Particularly, reduced volume of the left hippocampus is frequently associated with more severe PTSS [13,14] and predicts posttraumatic stress disorder development

[15]. Moreover, smaller hippocampal volumes at baseline have been related to greater reductions in PTSS in adults following an intervention [16].

Although MAT has been shown to acutely reduce emotional distress in pediatric cancer patients and survivors [11], 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.

Methods

1. Participants

Eighteen pediatric cancer patients or survivors participated in this 4-week prospective study (see **Table 1**). Participants were recruited from the Children's Hospital of Michigan Hematology/Oncology clinic, Kids Kicking Cancer (KKC), and local cancer support groups (e.g., Gilda's Club of Metro Detroit). Participants were eligible if they were: (1) between the ages of 5-17 years upon enrollment, (2) provided assent and had a parent/legal guardian provide consent and attend study sessions, (3) had a lifetime diagnosis of pediatric cancer that did not include the central nervous system, and (4) were free of MRI contraindications. The Wayne State University Institutional Review Board approved the study protocol.

Table 1. Participant demographics and clinical information.

Variable	*n* **(%)**	M (SD)	**Range**
Age upon enrollment (years)		10.7 (2.97)	5–17
Age at diagnosis (years)		5.6 (4.07)	1–17
Biological sex (females)	8 (44%)		
Treatment status	Treatment status	Treatment status	Treatment status
Current treatment (patient)	5 (27.8%)		
Past treatment (survivor)	13 (72.2%)		
Cancer diagnosis	Cancer diagnosis	Cancer diagnosis	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 American, Non-Hispanic	4 (22.2%)		
Other	2 (11.1%)		
Not reported	1 (5.6%)		
Annual household income			
$0-10,000	1 (5.6%)		
$10,000-20,000	1 (5.6%)		
$20,000-30,000	2 (11.1%)		
$30,000-40,000	3 (16.6%)		
$40,000-50,000	3 (16.6%)		
$50,000-60,000	0 (0%)		
$60,000-80,000	3 (16.6%)		

Variable	*n* **(%)**	M (SD)	**Range**
$80,000-100,000	1 (5.6%)		
$100,000-120,000	2 (11.1%)		
$120,000-140,000	1 (5.6%)		
Not reported	1 (5.6%)		
Baseline posttraumatic stress symptoms (PTSS)		17.37 (14.56)	3-64
Re-experiencing PTSS		4.22 (4.89)	0-19
Avoidance PTSS		2.11 (2.52)	0-7
Negative affect PTSS		4.11 (5.13)	0-22
Hyperarousal PTSS		5 (4.22)	0-16

PTSS were assessed using the adolescent self-report UCLA PTSD Reaction Index for DSM-5 [17].

2. Overall study design

Participants were interviewed about their cancer-related PTSS and underwent magnetic resonance imaging (MRI) at baseline. Participants then completed four, 60-minute in-person KKC classes, following the aforementioned standard procedures. KKC is a MAT that has been shown to lower pain and emotional distress in pediatric cancer and other populations, e.g., sickle cell, schoolchildren, adults with opioid use disorder [11,18,19]. PTSS were re-assessed following the completion of the four classes (**Figure 1a**).

Cancer-related PTSS

We computed an overall PTSS severity score at baseline and post-intervention, then change scores were computed to indicate response to intervention, i.e., PTSS at baseline minus post-intervention, such that higher scores indicate greater reductions in PTSS over time. PTSS subtypes (i.e., re-experiencing, avoidance, negative affect, hyperarousal) were also examined.

Gray matter volume analysis

See supplemental material.

Statistical Analyses

Related-Samples Wilcoxon Signed Rank Test was used to test for within-subjects significant changes in PTSS over time (baseline vs. follow-up). 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 (GM) vs. white matter (WM). All analyses were performed in SPSS v.27.0 [22] at$p$ <0.05 (two-tailed).

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 =0.31) or subtypes (p s>0.1) 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= 0.009, β =-0.77, p =0.004) and right (F (2,17)=4, p= 0.041, β =-0.65, p =0.019) hippocampal volumes were associated with more severe re-experiencing PTSS at baseline. 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= 0.031, β =-0.542,p =0.041; **Figure 1b,c**). This association was specific to GM (p =0.14) as compared to WM volume (p =0.47) and was driven by reductions in both re-experiencing *(*p =0.011) and negative affect (p =0.046) subtypes. Left hippocampal volume was not significantly associated with change in avoidance or hyperarousal PTSS subtypes (p s>0.5). Right hippocampal volume was not significantly associated with PTSS change scores, p =0.067.

Discussion

This study showed several notable results that support the role of hippocampal volume as a potential biomarker of PTSS severity and intervention response.

First, smaller hippocampal volumes were associated with more severe symptomatology at baseline, which is consistent with prior studies in adults [13,14]. In cancer patients and survivors, smaller hippocampal volume has been reported in adults [23] and children [24], suggesting sensitivity of the hippocampus to the neurotoxic effects of stress and cancer treatment [6,25].

Second, youth with smaller hippocampal volumes at baseline demonstrated greater reductions in cancer-related PTSS following a brief four-week MAT. Congruent with a recent meta-analysis, effects were specific to the left hippocampus, indicating that left hippocampal volume is more closely related to PTSS severity than the right [14]. We found hippocampal volume predicted reductions in re-experiencing and negative affect PTSS subtypes. Re-experiencing PTSS are particularly prevalent in both adult and pediatric cancer populations [6]. Prior research in breast cancer survivors linked greater re-experiencing PTSS to smaller hippocampal volumes [26]. Together, hippocampal volumes may serve not only as a promising biomarker of symptom severity, but also as a predictor of response to psychosocial interventions.

However, neither overall PTSS nor PTSS subtypes showed significant change over the four-week intervention. This may be due to small sample size, heterogeneity in cancer diagnoses, treatments, or age. It is also possible that four weeks was not a sufficient duration to assess change, as mindfulness-based interventions are typically eight weeks in length [27]. Future studies might benefit from a longer intervention period as well as a larger sample size to better assess the effects of MAT on PTSS.

Results of this preliminary study suggest that smaller hippocampal volume may be a predictor of more severe cancer-related PTSS and greater response to a four-week MAT in pediatric cancer populations. This extends prior research on effects of MAT and mindfulness-based practices on mental health in youth. Further, the findings contribute to a new understanding of the neural underpinnings of cancer-related PTSS in youth and highlight potential biomarkers that can be used to guide interventions.

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.

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Legends

Figure 1. Study timeline (A) left hippocampus (B) and association between baseline hippocampal volume and change in PTSS (C).

Supplemental Materials

Grey matter volume analysis

MRI data were processed following our prior work [20], using the automated cortical and subcortical extraction pipeline within Brainsuite software (v.18a) [21]. Following visual inspection, total volume (gray matter (GM) and white matter (WM)) of the left and right hippocampus (mm^3) were estimated. Total intracranial volume (GM, WM, and cerebrospinal fluid) was estimated for use as a covariate.