HEROES CIRCLE
POWER PEACE PURPOSE
KIDS KICKING CANCER

Heroes Circle Research Compendium

FIRST EDITION

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FIRST EDITION

Charach Global Center
27600 Northwestern Hwy., Suite 220, Southfield, MI 48034

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From the desk of Rabbi Elimelech Goldberg

Founder & Global Director, Heroes Circle | Kids Kicking Cancer;
Clinical Assistant Professor, Wayne State University School of Medicine

Dear Partner,

If you are reading this literature, I will assume that you are either a present or potential partner with our growing Heroes Circle®. The rapid expansion of our therapeutic model is based upon partnerships with extraordinary clinicians and health care institutions who are integrating evidence-based psycho-social support modalities into their standard therapy to reduce pain, trauma and anxiety, independent of pharmaceutical agents.

The Heroes Circle has been employing and evidencing non-contact Martial Arts Therapy as a cost saving, fun, safe and simple intervention for over twenty years. Children associate the martial arts as a symbol of empowerment. This allows us to use our breathing and meditative techniques to support them in controlling the pain and fear associated with illness and treatment. This journal is an amalgam of some of our publications and research. Our goal is to become a Standard of Care model of pain and anxiety mediation that will lower the pain of over one million children in the coming years.

We are very much looking forward to working together!

Power Peace Purpose,

Rabbi G.

Rabbi G.

Martin H. Bluth, MD, PhD

Global Medical Director, Heroes Circle | Kids Kicking Cancer; Chief of Blood Transfusion Medicine and Donor Services, Assistant Director of Clinical Laboratories and Director of Translational Research for the Department of Pathology at Maimonides Medical Center; Professor of Pathology at Wayne State University School of Medicine

Pain is a conundrum. It is a term cavalierly strewn around the medical condition as it pervades many corners of disease. It is ubiquitously applied to various chronic and acute disease states, yet it often remains ill-defined. We quantify its character with Likert scales and pain scores, address its quality, duration, depth and scope in every aspect of the human condition. Yet pain's essence eludes our grasp and our ability to control and reconcile with it remains evasive and vexing. Indeed, we have medications and anesthetics to dull, numb and modulate pain, but we often fall short of understanding on how it intercalates with our own locus of control.

Pain is a message we can choose not to listen to is a core tenet of Kids Kicking Cancer and our Heroes Circle programming. Those who participate in our programs demonstrate firsthand, the power and control one can exercise over his/her pain. The ability for one to regain and maintain ***Power, Peace, Purpose*** over one's self is demonstrated throughout this compendium. The publications contained within this collection show how one can surmount their pain, decrease their anxiety and depression often associated with continued subjection to painful states, and maintain healthy interactive family, social and productive lives. The neurophysiological changes that occur during a Breath Brake® further edify the reality that "breathing in the light and blowing out the darkness" can have profound positive effects on our perception of pain and related addictive behaviors that result thereof.

But this is just the beginning. Kids Kicking Cancer and our Heroes Circle endeavors continue to explore the benefits of its programming and interventions through interrogation by the Scientific Method and its application to various clinical disease states where pain exerts a profound effect on the human condition. I welcome you to join me as we continue to demonstrate the remarkable beneficial effects that our martial arts based meditative interventions exert on the human condition to heal.

Martin H. Bluth, MD, PhD

RESEARCH CONTRIBUTORS

INTERNAL STAFF

Elimelech Goldberg - Rabbi G
Founder & Global Director

Martin Bluth, MD, PhD
Global Medical Director

Cindy Cohen, MS, CCLS
Global Program Director

Jamila Carrington Smith
Chief Innovation Officer

Amanda Bluth, MSPH
Research and Grants Coordinator

RESEARCH PARTNERS

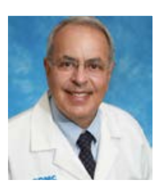
Hilary Marusak, PhD
Assistant Professor, Department of Psychiatry and Behavioral Neurosciences, Wayne State University

Mark K Greenwald, PhD
Associate Department Chair, Department of Psychiatry and Behavioral Neurosciences, Wayne State University

Jeffrey W Taub, MD
Chief of Oncology, Children's Hospital of Michigan; Professor, Department of Hematology Oncology, Wayne State University

Christine A Rabinak, PhD
Associate Professor, Department of Pharmacy & Health Sciences, Wayne State University

Robert Sapolsky, PhD
Professor of Neurology and Neurosurgery, Stanford University



Brian Berman, MD
Pediatric Hematology/Oncology, Children's Hospital of Michigan

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RESEARCH

MEDICAL FEATURES

ICON KEY

Pediatric Healing Program   School Program   Adult Healing Program

Pediatric Health, Medicine and
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Martial arts intervention decreases pain scores in children with malignancy

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Martin H Bluth[1,2]
Ronald Thomas[3,4]
Cindy Cohen[2]
Amanda C Bluth[5]
Elimelech Goldberg[2,4]

[1]Department of Pathology, Wayne State University School of Medicine, Detroit, MI, [2]Kids Kicking Cancer, Southfield, MI, [3]Children's Research Center of Michigan at Children's Hospital of Michigan, Detroit MI, [4]Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI, [5]Wayne State University, Detroit, MI, USA

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use:
http://youtu.be/ch1x5sVPDJk

Correspondence: Martin H Bluth
Department of Pathology, Wayne State University School of Medicine, Detroit, 540 E Canfield Street, MI 48201, USA
Tel +1 917 841 7409
Email mbluth@med.wayne.edu

Background: Martial arts intervention in disease has been mostly limited to adult inflammatory, musculoskeletal, or motor diseases, where a mechanical intervention effects positive change. However, the application and benefit to pain management in childhood malignancy are not well described. Here, we assess the effects of defined martial arts intervention in children with cancer with respect to their pain perception and management.

Methods: Sixty-four children with childhood malignancies were enrolled in a martial arts program, which encompassed both meditation and movement modalities. Pain scores (0–10) were recorded pre- and post- 1-hour session intervention. Pain scores were crossed by total visits and tabulated by whether participant pain reduced at least 1 unit, stayed the same, or increased in intensity immediately after (post) participation session. Differences in pain scores were further compared by age and sex.

Results: Prepain and postpain scale data were measured for 64 participants, 43 males (67.2%) and 21 females (32.8%), ranging from 3 years to 19 years. Preintervention and postintervention data were obtained for 223 individual session visits. Mean number of patient participation visits was 1.8±1.6 (range one to nine visits). Of 116 individual measured sessions where the participants began with a pain score of at least 1, pain intensity reduced ≥1 unit in 85.3% (99/116) of visits, remained the same in 7.8% (9/116), and increased in 6.9% (8/116). For the majority (96.3%; 77/80) of sessions, participants began with a prepain intensity score of at least 5–10 with reduction in pain intensity following the session. The overall mean pain score presession visit was reduced by ~40% (pre: 5.95±2.64 and post: 3.03±2.45 [95% CI: 2.34–3.50]; $P \le 0.001$). Median pain intensity scores had greater reductions with increased age of participants (3–6 years [−1], 7–10 years [−2], 11–14 years [−3], and 15–19 years [−4]).

Conclusion: Martial arts intervention can provide a useful modality to decrease pain in childhood cancer, with greater effect achieved with higher baseline pain scores and patient age. Martial arts intervention may improve patient compliance with respect to medical and surgical management, thus reducing disease morbidity and health care costs.

Keywords: martial arts, karate, cancer, pain, intervention, therapy

Introduction

Cancer continues to dominate the health care landscape.[1] Although administration of pharmacological agents constitutes the major intervention in this disease space, other "nondrug" therapies constitute a significant component of the psychosocial–economic opportunity with respect to treatment. Much of the interventions with regard to cancer treatment, vis-a-vis both pharmacological and nonpharmacological modalities, focus on controlling the pain associated with this disease. Indeed, cancer pain accounts for considerable costs and may also contribute to noncompliance either as a result of treatment regimens or patients' quality of life.[2–4]

Pediatric cancer contains another layer of complexity in that the patient often refers to the unit of the father, mother, and child, and as such, may affect compliance to therapy, the perception of pain, and quality of life. Other variables including the patient's other relatives and belief structure, provide additional considerations.[5–8] Various modalities have been used to address pediatric cancer pain. Although pharmacological options have been used to decrease pediatric pain, barriers to successful implementation include parents' reluctance to their child receiving pain medication, inadequate information/education pertaining to physician medication orders, subjective pain perception and severity scores, and fear of addiction or tolerance to pain medication among others.[8–10] Insurers are eager to adopt interventions for controlling cancer pain (pediatric and adult), since this would facilitate considerable cost saving to the health care industry as a means to increase patient compliance to therapy and disease management as well as to decrease other morbidities.[11–14]

The application of martial arts in health maintenance has been well documented. Both physical (Karate, Tai Kwon Do, etc) and meditative (Tai Chi and Chi[Qi] Gung, etc) modalities within the scope of martial arts have been shown to increase flexibility, range of motion, mental focus, and decrease anxiety and stress.[15–17] Martial arts facilitate control over oneself and include different aspects of metered breathing, guided imagery, and physical as well as mental conditioning to overcome challenges. The positive effects of martial arts in disease states have also been described. Recent studies have shown that rheumatoid arthritis patients who practiced Tai Chi 50 minutes/week for 12 weeks had decreased pain and fatigue when compared with routine care.[18,19]

Similarly, patients suffering with osteoarthritis or fibromyalgia, where there are less effective disease-modifying agents than for rheumatoid arthritis, can also benefit from Tai Chi.[20–22] In those studies, implementation of distinct Tai Chi regiments, either short form or long form (which pertains to the number of postures per form), has been correlated with positive findings pertaining to improved muscle strength, endurance, reduced stress, psychological well-being, flexibility, and muscle control. Even in pilot studies where there were no observed differences between Tai Chi and control groups over a 4–8-week regimen,[23] participants generally "preferred Tai Chi to their previous physiotherapeutic intervention, finding it more useful and more enjoyable". Furthermore, the implementation of Tai Chi to other diseases including Parkinson's[24] and heart diseases[25] has also been reported. Regarding malignancy, a recent meta-analysis demonstrated positive effects of Tai Chi and Qigong in adult cancer patients in improving their quality of life and decreasing markers of inflammation (C-reactive protein and cortisol).[26]

Although there are reports of the application of martial arts in other disease states with demonstrations of beneficial effects, here we describe the effects of martial arts as an interventional therapeutic modality to reduce pediatric cancer pain. This program is further adaptable to hospital and clinic settings as well as noncancer pediatric disease space, thus providing widespread accessibility toward the control and mitigation of pediatric pain.

Methods

Sixty-four children with childhood malignancies were enrolled in the martial arts therapy program, which encompassed both the meditative aspects of martial arts and the actual movements and techniques used in that discipline over the course of 12 months. The intervention was administered by specially trained martial arts instructors according to the standard operating procedures of the organization Kids Kicking Cancer (www.kidskickingcancer.org) and patient consent was obtained prior to intervention. Each program consists of a 1-hour session, where patients are exposed to a mix of martial arts-based therapeutic interventions, either individually or in group setting. The session begins with identifying each child participant's (presession) pain rating as well as location of pain and cause where applicable (ie, "my pain was 7/10 after having chemotherapy, line/catheter/port placement, and/or injections", etc). Pain scores are recorded using an 11-point (0–10) verbal and/or continuous visual analog scale. The visual analog scale is a psychometric response scale commonly used in questionnaires to measure pain as an instrument for subjective characteristics or attitudes that cannot be directly or objectively measured. The participant begins with a "body scan" in which children lie down and begin to meditate, focusing upon the sensation of their breath. After a few moments (times differ based on the age and attention level of the group), the students are asked to imagine themselves perceiving their bodies beginning from the top of their head and proceed downward through their body relaxing the different muscle group on the voice direction of the "sensei" (martial arts instructor). The "body scan" also helps each participant focus on and become cognizant of each body part with respect to pain/fear/frustration and function and gently allows any unpleasant sensations to flow out of their body. The session continues with karate style martial arts movements modified for each patient according to his or her capabilities. After 30 minutes, participants rehydrate and discuss how they have used their breathing and meditation therapeutic techniques during that week to "bring in the light and blow out the darkness" of their procedures or medical situations. Each child defines his or her "darkness" (ie, "IV placement in the hand vein") and is invited to share with the class how they triumphed during the week using their "light" (via breath/meditation) to push out the darkness. This provides an individualized and collective patient empowerment as well as affirmation of successful pain management (participants are referred to as "powerful martial artists" and that "pain is a message that we do not have to listen to").

Each class incorporates a martial arts "Breath Brake®" – a modality that incorporates three cycles of "breathing in (metered inhalation with slight lifting of the chest/body)" for 3 seconds, "holding (maintaining)" the breath for 3 seconds, and "breathing out (metered exhalation, where chest/body is slightly lowered and relaxed)" for 3 seconds, each time envisioning "breathing in the light and breathing out the darkness". The remaining 30 minutes include individualized or small group sessions, which focus on different aspects of martial arts movements and exercises, and further internalizing the concepts via physical touch points of parenthetically breaking the pain with punches and kicks as well as allowing the pain to pass through the individual by using the image of the breath to pass through and relax the area in pain. Because children on chemotherapy often have brittle bones, there are never any breaks or sparring involved in the program. However, the children do punch or kick a soft rubber target mitt when able. As the martial arts are focused on imagery, the children are invited to see their target as their disease, pain, anger, or any "darkness" the children choose. The children are asked to image themselves "destroying" their disease or whatever they define as the "darkness" and "see" it shatter with perceived reduction.

As the martial arts are "ritually oriented", the children have a special bow and "karate yell" that they are asked to do several times during the class. At Kids Kicking Cancer, the children bow and call out the mantra "Power, Peace, Purpose"™. "Power" represents each child's ability to bring in a powerful martial arts energy. "Peace" represents how a child can blow out the pain, fear and sadness that he/she may face. "Purpose" represents each child's ability to project their triumph and "Teach the world" that pain, stress and adversity can be overcome. Because the pediatric patients face such darkness, their parents, caregivers, nurses, and doctors also become participants and also learn from them how to face down the stressors in their adult lives, further augmenting the positive influence of the program. The session concludes with another round of "power breathing" and post session pain scores. These studies were approved by the participating institutional review boards of Brooklyn Hospital Medical Center, Columbia Presbyterian Medical Center, and Maimonides Medical Center.

Statistical analyses

Patient demographic and descriptive visit data were assessed using mean values, standard deviations, median values, modes, ratios, and proportions. The range of pain scores (overall ≥1 and within categories from 1 to 10) was crossed by total visits and tabulated by whether participant pain reduced at least 1 unit, stayed the same, or increased in intensity immediately after (post) participation session. From our perspective, a minimally clinically important reduction in pain is assigned to any lowering of pain level that children are able to accomplish. Furthermore, although any reduction in pain is clinically worthwhile in children, achieving greater reductions could be considered more important in pain relief than reductions in lower scores.

The percentage of change in pain intensity after session was recorded to depict whether pain intensity reduced, stayed the same, or increased pre-/postvisit, where pain intensity reduced by at least 1 unit postintervention with ranges of pain intensity, minimum and maximum values, and interquartile ranges. Nonparametric Wilcoxon signed rank test for related (paired) samples was conducted for those which reported at least a pain intensity score of 1 presession with postsession scores. Mean percent change scores were also table reported by prepain score category of pain (on a scale of 1–10 of increasing pain) by visits. Median prepain and postpain intensity change scores were further compared between four age categories using a nonparametric Kruskal–Wallis procedure, followed by pairwise comparisons conducted using a nonparametric Mann–Whitney U test. Age groups were created by using ~25% cutoffs in the frequency age range. Nonparametric Mann–Whitney U test compared prepain and postpain difference scores by sex. Nonparametric Spearman's Rho correlation coefficient was conducted to examine if a possible relationship existed between prepain and postpain intensity scores and age. Statistical significance was considered achieved at $P \leq 0.05$. All statistical procedures were conducted using SPSS Version 22, IBM Corporation (Armonk, NY, USA).

Results

Weekly pre- and postpain scale data were measured for 64 participants, 43 males (67.2%) and 21 females (32.8%; Table 1). Their ages ranged from 3 years to 19 years, with a median of 11 years, a mean of 11.2±3.9 years, and a mode of 12 years, and represented varied ethnicities (Caucasian 31%, African American 28%, Hispanic 33%, and Asian 5%). Pre- and postintervention data were obtained for 223 individual session visits. In all, 48.0% (107/223) of participants reported no pain (zero) prior to their presession, who were excluded from subsequent analysis. Data analyses therefore concentrated on those participants and visits where prepain intensity scores were recorded as ≥1. Sessions occurred weekly; however, participant pain scores were not measured every week, due to holidays and some absences. Mean number of patient participation pre- and post- (same day) measured visits was 1.8±1.6, with a range of visits from one to nine visits.

Participants began their session visits ranging in pain scale score from ≥1 to as high as 10. Of 116 individual measured sessions where the participants began with a pain score of at least 1, pain intensity reduced ≥1 unit in 85.3% (99/116) of visits, increased in 6.9% (8/116), and remained the same in 7.8% (9/116; Figure 1).

Table 2 represents the range of pain intensity scores for participants who had a pain score of 1 or greater prior to their visit (overall ≥1 and within categories from 1 to 10) crossed by total visits and tabulated by whether participant pain reduced at least 1 unit, stayed the same, or increased in intensity after (post) weekly participation session. In total,

Table 1 Participant demographics

Participants	n=64
Sex	
Male	43/64 (67.2%)
Female	21/64 (32.8%)
Ethnicity	
Caucasian	20/64 (31.3%)
African American	18/64 (28.1%)
Hispanic	21/64 (32.8%)
Asian	3/64 (4.7%)
Age (years)	
Mean ±SD age	11.2±3.9
Median age	11.0
Mode age	12.0
Age range	3–19
Session visits	
Mean ±SD no of visits	1.8±1.6
Median no of visits	1.00
Range visits	1–9

Table 2 Pain reduced at least 1 unit on pain scale immediately after (post) weekly participation session, n (%)

Prepain score before session	Total no of visits	Yes	No	Stayed the same
1	12	2 (17)	4 (33)	6 (50)
2	3	2 (67)	1 (33)	0
3	9	8 (89)	1 (11)	0
4	12	10 (83)	2 (17)	0
5	9	9 (100)	0	0
6	9	9 (100)	0	0
7	24	22 (92)	0	2 (8)
8	18	17 (94)	0	1 (6)
9	14	14 (100)	0	0
10	6	6 (100)	0	0
Total (>1)	116	99 (85)	8 (7)	9 (8)

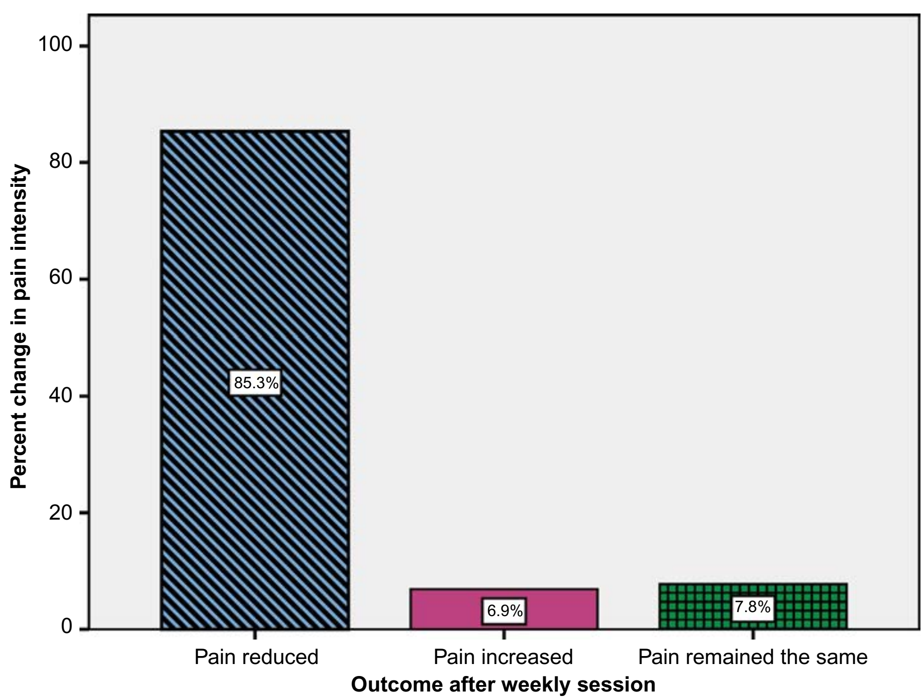

Figure 1 Pain intensity outcome after weekly session (n=116).

for all visits 85% of participants demonstrated at least one point reduction in pain, 7% demonstrated an increase, and 8% remained the same. Of these, the majority of individual visits started with pain scale scores of 3 or greater, with the largest pain intensity scores presession being in the range of 7–9 (48.2%; 56/116 visits). Interestingly, the majority (96.3%; 77/80) of individual sessions where participants began with a prepain intensity score of ≥5, reduced in pain intensity following the session; in these participants, only three remained the same and none increased in pain intensity postsession.

Table 3 represents the overall mean prepain and postpain scores of session visits for those who began the session with at least a pain score of 1 or higher. The overall mean pain score presession visit (n=116) was 5.95±2.64, which reduced to 3.03±2.45 postsession. The median value presession was 5.00 and postsession was 3.00. The interquartile value of pain intensity reduced from prevalues of 4.00 (25th percentiles) and 8.00 (75th percentiles) to postvalues of 1.00 and 5.00, respectively. The overall median pain score significantly reduced from 5.00 to 3.00 (40% reduction; ≤0.001).

Table 3 Participant visits where pain reduced at least 1 unit

	Pain before	Pain after
N (visits)	116	116
Mean	5.95	3.03
Median	5.00	3.00
Mode	7.00	0.00
Standard deviation	2.64	2.45
Difference between minimum and maximum in range	9	8
Minimum	1	0
Maximum	10	8
Percentiles 25	4.00	1.00
Percentiles 75	8.00	5.00

Table 4 Mean percent change in pain scale scores immediately after (post) weekly participation session

Prepain score before session	Total number of visits	Mean ±SD
≥1	116	−24.4%±1.4%
≥2	102	−51.7%±41.2%
≥3	99	−52.8%±36.0%
1	12	+2.1%±3.5%
2	3	−16.7%±1.4%
3	9	−44.4%±50.0%
4	12	−50.0%±56.4%
5	9	−67.5%±32.0%
6	9	−57.4%±32.4%
7	24	−43.5%±30.8%
8	18	−57.6%±28.8%
9	14	−57.1%±28.5%
10	6	−58.0%±30.3%

Notes: (−) sign indicates the mean percent reduction in pain; (+) sign indicates the mean percent increase in pain.

Table 5 Change from highest presession to lowest postsession pain scores

Lowest postsession pain score										
Number of children with increased pain scores (bolded numbers)										
Highest presession pain score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
1	2	6	**0**	**0**	**0**	**0**	**0**	**1**	**3**	12
2	2	0	0	**0**	**0**	**1**	**0**	**0**	**0**	3
3	2	2	4	0	**0**	**1**	**0**	**0**	**0**	9
4	5	0	3	2	0	**1**	**0**	**1**	**0**	12
5	3	1	2	2	1	0	**0**	**0**	**0**	9
6	2	1	1	2	1	2	0	**0**	**0**	9
7	4	0	1	2	5	7	3	2	**0**	24
8	3	0	4	3	2	2	3	0	1	18
9	2	2	1	0	2	2	3	2	0	14
10	0	1	3	0	0	0	0	1	1	6
Total	25	13	19	11	11	16	9	7	5	116

Table 4 represents the mean percent change in pain intensity scores after (post) weekly session visit. Overall, where initial pain scores were ≥1 (116 visits), pain was reduced by a mean percent of 24.4%±1.4%. Where initial pain scores were ≥2 (102 visits), pain reduced by a mean percent of 51.7%±41.2%, and where beginning pain score was ≥3 (99 visits), pain reduced by a mean percent of 52.8%±36.0%. Prepain intensity scores that began at 4 or higher experienced mean percent reduction in postpain scores ranging from 43.5% to 67.5%.

Table 5 depicts the individual session changes that occurred for all 116 visits where the relationship of each presession to postsession pain score is reported in an individualized manner for each visit. For example, 24 participant sessions began with a prepain score of 7. Of these, four participants reported a reduction of pain to 0, one participant reported a reduction of pain to 2, five participants reported a reduction of pain to 4, seven participants reported a reduction of pain to 5, three participants reported a reduction of pain to 6, and two participants remained the same from their presession score of 7. No participants reported an increase in pain. The bolded values represent any prepain participant's score that increased after treatment. Only eight of 116 total sessions, representing 7% of the study participants, showed an increase from prepain scores, and nine participants remained the same as their preintervention pain scores. Thus, >85% of those studied demonstrated a reduction from prepain scores after this intervention.

When pain intensity scores were further compared between four age categories (3–6 years, 7–10 years, 11–14 years, and 15–19 years; Table 6), median pain scores reduced 1 unit through each successive older age group, beginning at a median of −1.00 in the lowest age group (3–6 years) and reducing to a median of −4.00 in the oldest age group (15–19 years), $P \leq 0.001$. Median prepain

Table 6 Reduction in pain scores by age groups

Age group (years)	Median	Mean (standard deviation)	95% CI
3–6	−1.00	−1.83 (1.9)	−3.9 to 0.2
7–10	−2.00	−2.84 (3.4)	−4.1 to −1.6
11–14	−3.00	−2.94 (2.0)	−3.6 to −2.3
15–19	−4.00	−4.10 (3.5)	−5.4 to −2.8
Overall	−2.00	−3.19 (3.0)	−3.8 to −2.6

and postpain difference scores between males (−3.00) and females (−3.00) were identical (data not shown). In addition, all three ethnic groups experienced reductions in their mean prepain and postpain scores intervention; Caucasians reduced their pain scores by almost 3 units (2.99±3.01), African Americans by 2½ units (2.47±3.19), and Hispanics recorded slightly less reductions in pain scores (1.76±2.78); however, the differences were not statistically significant (>0.05; data not shown).

Discussion

The application of martial arts-related regimens in disease states is not well understood. Many of the studies that assess the effects of martial arts centralize around movement anomalies, which may be subject to mechanical or inflammatory processes in addition to its well-known effects to improve general psychological well-being.[15–20,23,24] Recent data on the effects of biological effects of martial arts have also been described. To this end, Ho et al[27] reported an increase in blood CD34+ progenitor cells in those engaged in the practice of Tai Chi suggesting its value as an antiaging therapy, while Chyu et al[28] reported an increase in serum insulin growth factor 1 levels, facilitating promotion and maintenance of muscle mass and neuronal function in overweight/obese premenopausal women who participated in a martial arts exercise intervention.[29,30]

The application of martial arts intervention in cancer has also been described. Recent data suggest that such modalities can be valuable as a means to improve physical and psychological quality-of-life parameters in their relation to treatment.[26] In those studies, the authors conduct a meta-analysis of the literature, which presents reports that martial arts intervention in cancer patients reported 1) less depressive symptoms,[31] 2) stability of insulin levels,[32] 3) improvement in self-esteem[33] and social/family well-being,[34] 4) strength and flexibility,[35] 5) cognitive function,[36]6) survival,[34] and 7) inflammatory/metabolic markers such as C-reactive protein and cortisol[36,37] compared with control groups among a variety of adult malignancies. Although some reports did not demonstrate any statistically significant changes in select parameters,[38] there were demonstrable positive trends.[37]

Our studies are the first to assess the effect of martial arts intervention in a pediatric population where the participants predominantly suffered from cancer-related pain. In evaluating pre- to post-test scores, it is important to acknowledge the possibility of "regression to the mean" where the study group will eventually trend to the population mean. However, the regression can occur in either direction. In our case, we have demonstrated that the intervention consistently reduced the perception of pain in an ethnically diverse pediatric population and that the major pain reduction was observed when the baseline preintervention scores 1) were >3, 2) were most robust when pain scores were >5, 3) positively reduced preintervention pain scores in >85% of the participants, and 4) had better pain score reductions with increased age. Furthermore, we have shown an overall reduction in reported pain scores of ≥40% as a result of this program.

It is interesting to note that this program is beneficial in the pediatric population among various age groups. Pain in the pediatric population is unique as it encompasses various stages of development and thus may translate pain registration and reporting differently as children mature. As many as 40% of children and adolescents complain of pain that occurs at least once weekly, and chronic pain affects at least 15%–20% of children. Furthermore, just as chronic pain is more prevalent in women than men, girls report more pain than boys.[39] Each year, 1.5 million children, irrespective of malignancy, undergo surgical procedures, and many receive inadequate pain relief; in 20% of cases, the pain can become chronic thus creating a lifelong medical issue.[40,41] On a larger scale, failure to intervene early in children's pain may lead to impairment in functioning and disruption in families. Unaddressed pain heightens anxiety and fear, which, in turn, can increase perception of pain.[42]

Perception of pain in pediatric medicine is complex and entails physiological, psychological, behavioral, and developmental factors. Although health care professionals often prefer practical methods, which reliably track the child's pain experience and pain control over time, researchers tend to focus on tools which are proven for reliability with different observers.[43] To this end, three main methods are currently used to measure pain intensity: self-report, behavioral, and physiological measures. Self-report measures are optimal and the most valid. Both verbal and nonverbal reports require a certain level of cognitive and language development for the child to understand and give reliable responses. Children's capability to describe pain increases with age and experience and changes throughout their developmental stages.[44] An additional variable often promulgated in the medical milieu is that children do not feel pain the way adults do[45] and that pain in adolescent patients is often underestimated and under treated[46] since adolescents tend to minimize or deny pain, especially in front of parents and friends, and some adolescents regress in behavior under stress.[45] In light of this, it is thus quite remarkable that this program is able to engender significant pain reduction in a wide range of age groups (3–19 years) and that older patients, in contrast to conventional thinking, actually demonstrated a more robust reduction to pain, thus providing applicability to a large proportion of the childhood population in pain.

Although there have been reports of other alternative modalities used in childhood cancers including faith healing, massage, vitamins, chiropractic, and relaxation,[47] many of these interventions were instituted to cope with disease symptoms and side effects of medications and were often incorporated when families were dissatisfied with conventional medical care.[48]

A unique strength of this program and the therapeutic intervention it provides the concept of "teaching the world" a psychosocial projection of one's own power to enable another in pain to surmount such, thus facilitating a groupthink mentality, which has been reported as a successful value-added component in other disease states,[49] where those in pain help and empower each other to decrease the registration of pain. The distillation of this intervention "Power, Peace, Purpose"™ (the organization's tag line/ brand) thus becomes a mantra for the patient to incorporate these concepts at any time, during and after the intervention, where pain in any definition needs to be addressed. Furthermore, the program has been incorporated into the medical landscape of numerous children's hospitals in the US, as well as other countries, and is thus well received in the allopathic domain as it pertains to pediatric cancer management.

There are, however, limitations to our observations that would benefit from additional study. The degree to which intervention should be instituted and the frequency, which would be considered ideal, require further study. These studies were derived from sequential categorization of pain scores from participants in the program collected as they participated, without any a priori power analysis or detailed criteria for patients' involvement. A successful intervention would likely also be bolstered by the reinforcement of participating family members, treating clinicians, friends, and other children with cancer. Whether these collective components or individual isolated variables would contribute to a participant being a more likely "responder" to the intervention, as we have observed in ~85% of our participants, or whether the physical (hard) or meditative (soft) martial arts intervention approaches are more suitable for one participant over another is unknown. These comprise opportunities identified from our current studies in that such variables were not accounted for and may be valuable to incorporate into a streamlined intervention for more optimal pain reduction. In addition, the duration of intervention may be improved by initially increasing the frequency (per week or month) with subsequent maintenance as the patient becomes well versed with the modalities and can integrate them into care in a nonclass setting. Furthermore, the short-term duration of interventions in most of the participants in the current studies (less than four sessions in most) and the lack of consecutive visits may reduce the long-term effects of Qigong/Tai Chi/martial arts on cancer pain; thus, the optimal duration of such intervention has yet to be defined.

In alignment with other alternatives, including Nia and Hypnosis, which are incorporated into diseases including malignancy,[50,51] it would be ideal to maximize such martial arts-based therapeutic interventions since they are less costly, yet empowering, which synergize and can likely augment conventional allopathic therapy toward the benefit of the patient.

Conclusion

Martial arts-based therapeutic interventions can be quite effective in mitigating pain in childhood cancer. Such interventions can be empowering and well received by the patient and his or her family, thus further facilitating its beneficial effects. Additional studies to determine duration and frequency of participation in addition to cost reduction and objective reporting (laboratory, inflammatory, and metabolic markers) can help streamline effective integration of the martial arts into pediatric oncology and other medical practices.

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Disclosure

The authors report no conflicts of interest in this work.

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

Hilary A. Marusak[1] · Allesandra S. Iadipaolo[1] · Felicity W. Harper[2,3] · Farrah Elrahal[1] · Jeffrey W. Taub[4,5] · Elimelech Goldberg[4,6] · Christine A. Rabinak[1,7,8]

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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

✉ Hilary A. Marusak
hmarusak@med.wayne.edu

1 Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Ave., Suite 2190, Detroit, MI 48202, USA

2 Population Studies and Disparities Research Program, Karmanos Cancer Institute, Detroit, MI, USA

3 Department of Oncology, School of Medicine, Wayne State University, Detroit, MI, USA

4 Department of Pediatrics, School of Medicine, Wayne State University, Detroit, MI, USA

5 Children's Hospital of Michigan, Detroit, MI, USA

6 Kids Kicking Cancer, Southfield, MI, USA

7 Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA

8 Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, MI, USA

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.

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 lifetime 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

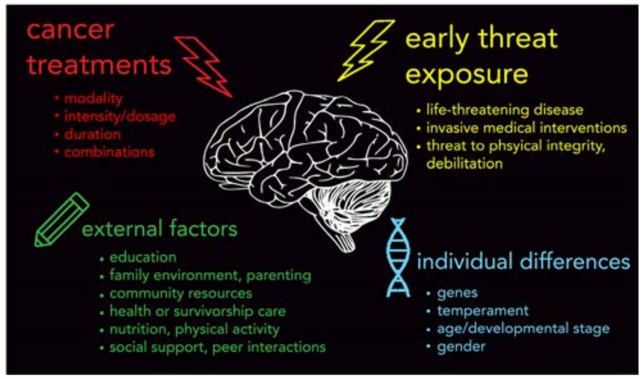

Fig. 1 Top: Early threat exposure and cancer treatments are both developmental insults that can alter neural development and contribute to the range of cognitive, behavioral, and emotional late and long-term effects reported in childhood cancer patients and survivors. Bottom: various potential external (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

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”, “medullobastoma” “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

Table 1 Review of neuroimaging studies in child and adolescent cancer survivors

First author	Year of publication	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])
1 Li et al.	2017	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]
2 Baron Nelson et al.	2016	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]
3 Cheung et al.	2016	The Lancet Haematology	190	190	__	ALL	10-18	4.9 [2-10]	7.35 [6-9]
4 Kesler et al.	2016	Brain Connectivity	70	31	39	ALL	11 (3.4)	5.4 (3.7) [2-14]	2.92 (2.58) [0.5-9.25]
5 Krull et al.	2016	Journal of Clinical Oncology	218	218	__	ALL	13.8 (4.8)	6.6 (4.5)	7.7 (1.7)
6 McEvoy et al.	2016	Neuroimage Clinical	47	47	__	Cerebellar tumor	9.7 (4.8)	>2	[0-1]
7 Oh et al.	2017	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)
8 Scantlebury et al.	2016	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]
9 Zou et al.	2016	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]
10 Conklin et al.	2015	Journal of Clinical Oncology	68	68 (n = 34 intervention group, n = 34 wait-list con-trols)	__	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)
11 Khajuria et al.	2015	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)
12 Liu et al.	2015	Neuro-oncology	64	32	32	LGG (subtentorial n = 19, supratentorial n = 13)	13.99 (3.03) [8.42-19.12]	subtentorial: 7.22 (3.12) [1.60–12.33], supratentorial: 3.86 (2.26) [1.05–8.41]	subtentorial: 5.58 (3.95) [0.59-13.26], supratentorial: 11.89 (2.52) [8.82-16.76]
13 Robinson et al.	2015	Child Neurosychology	32	17	15	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]	6.94 (2.41) [2.06–11.62]	5.29 (2.83) [2.13–10.92]
14 Rueckriegel et al.	2015	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)

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15 Bhojwani et al.	2014	Journal of Clinical Oncology	369	369	__	ALL	[1-18]	Not stated	Not stated
16 Duffner et al.	2014	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]
17 ElAlfy et al.	2014	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 83protocol: 7.96 (1.98)
18 Horska et al.	2014	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
19 Jacola et al.	2014	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)
20 Kesler et al.	2014	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]
21 Riggs et al.	2014	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]
22 Robinson et al.	2014	Neuropsychology	32	17	15	Brain tumor: pilocytic astrocytoma (n = 9), posterior fossa MB (n = 4), dysembryoplastic neuroepithelial tumor (n = 3), and craniopharyngioma (n = 1)	12.60 (2.48) [8-16]	6.94 (2.41) [2.06–11.62]	5.29 (2.83) [2.13–10.92]
23 Badr et al.	2013	Oncology letters	25	25	__	ALL	12.9 (3.2) [8.5-20]	6.9 (3.04) [2.5-13]	>5
24 Genschaft et al.	2013	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]
25 Kuper et al.	2013	The Cerebellum	23	12	11	Cerebellar tumor	11.1 [6-17]	Not stated	[0-1]
26 Wolfe et al.	2013	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]
27 Hosseini et al.	2012	PloS One	59	28	31	ALL	12.0 (4.6) [5.0–19.8]	Not stated Not s+ O13tated	4.19 (2.55) [0.5-10.5]
28 Zou et al.	2012	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
29 Ashford et al.	2010	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)
30 Ficek et al.	2010	Brain Edema XIV	45	45	__	ALL	[4-17]	Not stated	[6-12]
31 Kesler et al.	2010		59	28	31	ALL	12.0 (4.6) [5.0–19.8]	Not stated	4.19 (2.55) [0.5-10.5]

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		Brain Imaging and Behavior							
32 Robinson et al.	2010	Pediatric Blood and Cancer	15	8	7	ALL	14.07 (2.32)	4.94	6.46
33 Aukema et al.	2009	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]
34 De Smet et al.	2009	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
35 Reddick et al.	2009	American Journal of Neuroradiology	197	197	__	ALL	[1.0-18.9]	5.3	N/A (active treatment). Average time between two MRI scans, 0.325 (.067)
36 Carey et al.	2008	American Journal of Neuroradiology	23	9	14	ALL	15.17 (5.48) [7.75-25.76]	5.17 (2.96) [1.43–9.36]	9.95 (5.13) [3.48–16.96]
37 Kirschen et al.	2008	Behavioural Neurology	24	12	12	Cerebellar PA	12.5 (4.1) [6-19]	Not stated	5.5 (3.1)
38 Zhang et al.	2008	Neuroimage	27	13	14	Posterior fossa brain tumor	12.3 (3.1) [7-17]	Not stated	Not stated
39 Qiu et al.	2007	International Journal of Radiation Oncology Biology Physics	44	22	22	MB	12.1 (4.6)	8.1 (4.6)	3.9 (2.9)
40 Khong et al.	2006	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)
41 Mabbott et al.	2006	Neuro-oncology	16	8	8	MB	9.98 (2.90)	7.48 (3.87)	2.5 (0.72)
42 Qiu et al.	2006	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]
43 Reddick et al.	2006	Cancer	145	112	33 siblings	ALL	9.8 (3.1)	4.1 (2.6)	6.0 (3.5)
44 Shan et al.	2006	Magnetic Resonance Imaging	58	58 (Group A decreased NAWM volume n = 39, Group B increased NAWM volume n =	__	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]
45 Konczak et al.	2005	Brain	36	22	14	Cerebellar tumor	[10-28]	[1-17]	8.2 [>3]
	2005a, b	Neuro-oncology	52	52	26	MB	Not stated	8.3 [3.4-20.0]	2.5 [0.2-7.9]

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46 Reddickck et al.									
47 Reddick et al.	2005a, b	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
48 Reddick et al.	2005a, b	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
49 Zou et al.	2005	Neuroimage	43	16	16 adults (ages 20-35), 11 siblings (ages 8-16)	n = 8 ALL, n = 8 brain tumor (glioma, astrocytoma, ependymoma, MB	13.2 (2.4) [9-17]	6.27	5.4 (2.3) [2-9]
50 Hill et al.	2004	Pediatric Blood and Cancer	20	10	10	ALL	[6-14]	[3-5]	>3
51 Leung et al.	2004	Neuroimage	32	16	16	MB	11.1 (4.2) [3.2-18.6]	8.8 (4.6) [2.7-17]	3.1 (1.8) [0.8-6.3]
52 Mulhern et al.	2004	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]
53 Nagel et al.	2004	American Journal of Neuroradiology	25	25	__	MB	4-12	8.27	0.31
54 Chu et Al.	2003	Radiology	23	23	__	ALL	Not stated	1-14	N/A (active treatment)
55 Khong et al.	2003	American Journal of Neuroradiology	18	9	9	MB	10.8 [3-19]	7.8 [3-14]	3.6 [1-6]
56 Pääkkö et al.	2003	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)
57 Reddick et al.	2003	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 =	12.8 [7.1–18.8]	6.5 [1.7–14.8]	5.7 [2.6–15.3]
58 Palmer et al.	2002	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)

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59 Mulhern et al.	2001	Journal of Clinical Oncology	42	42	__	MB	12.6 (4.2)	8.2 (3.8)	4.0 (2.7)
60 Levisohn et al.	2000	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]
61 Paakko et al.	2000	Pediatric Blood and Cancer	33	33	__	ALL	Not stated	6.2 [2.1-15.0]	N/A (active treatment)
62 Reddick et al.	2000	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]
63 Mulhern et al.	1999	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)
64 Harila-Saari et al.	1998	Cancer	32	32	__	ALL	13.2 [8-24]	5.3 (3.5)	5.0 (0.4)
65 Reddick et al.	1998	Magnetic Resonance Imaging	94	77	17	Brain tumor	5-21	6.9 [3.3-15.6]	5.1 [1.2-10.6]

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 Li et al.	MB: Surgical resection, CSI, and CT, PA: Surgical resection alone	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- whereas CBF was not related to IQ.
2 Baron Nelson et al.	CT	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 diffusivity and decreased FA) were apparent in memory and executive functioning areas in patients. Particularly, low

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							inhibition scores correlated with heightened mean diffusivity in prefrontal areas in patients.
3 Cheung et al.	CT	DTI	Longitudinal	Fine motor dexterity	IQ, executive function, processing speed, attention, memory	—	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).
4 Kesler et al.	Intrathecal CT standard dose (n = 23) and high dose (n = 9)	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 the ALL group. Decreased connectivity within neighboring brain regions in young survivors of ALL may be related to reductions in local information processing efficiency.
5 Krull et al.	CT	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,

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							and with alterations in frontostriatal white matter microstructure.
6 McEvoy et al.	Surgical resection	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 cerebellar peduncle were still evident at one year post-surgery.
7 Oh et al.	Surgical resection (100%), adjuvant CT (MB patients)	Structural MRI, DTI	Cross-sectional	Ataxia, fine motor function	—	—	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.
8 Scantlebury et al.	CSI (n = 30), surgery with or without focal radiation (n = 29)	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 processing speed scores compared to healthy controls, which was related to reduced integrity of the right optic radiations.

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9 Zou et al.	Surgical resection, CRT, and CT	Task-based fMRI (5 tasks probing reading-related neural activation); 3 fMRI and reading evaluations at 1 year intervals.	Longitudinal	—	Reading abilities, continuous processing	—	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.
10 Conklin et al.	CT only (n = 42), CSI and CT (n = 15), CRT and CT (n = 6), CT+ BMT and TBI (n = 5)	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 reduced compared to pre-intervention activation.
11 Khajuria et al.	Surgical resection, CRT, and CT	Structural MRI (post-resection)	Cross-sectional	—	IQ, attention, working memory, and visual motor coordination	Health-related quality of life	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.
12 Liu et al.	Neurosurgery (n = 25), CT (n = 10)	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

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							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.
13 Robinson et al.	Surgical resection (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/interalizing 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 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.
14 Rueckriegel et al.	MB: Surgical resection, CSI and CT, PA: Surgical resection	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 dysfuntion in pediatric posterior fossa tumor survivors.
15 Bhojwani et al.	CT (5 courses of high-dose MTX and 13-25 doses of triple intrathecal therapy)	Structural MRI	Longitudinal	—	—	—	High MTX exposure was associated with increased risk of leukoencephalopathy. Leuekoencephalopathy was evident in all symptomatic patients and 1 in 5 asymptomatic patients, and persisted in 58% of symptomatic and 74% of asymptomatic 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

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							half of symptomatic patients at the end of therapy.
16 Duffner et al.	2 CT protocols: P9201 (fewer CNS-directed treatment days during intensive consolidation, n = 24) and P9605 (intense CNS-directed therapy, n = 35)	Structural MRI (at least 2.6 years after the end of treatment)	Cross-sectional	__	IQ, perceptual organization, processing speed, visuomotor integration, attention, continuous performance	__	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.
17 ElAlfy et al.	CT protocols: modified BFM 83, BFM 90, or CCG.	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 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.
18 Horska et al.	CRT (n = 5 with neurosurgery, n = 2 with neurosurgery and CT, n = 1 with CT, n = 1 with CRT alone)	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	__	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.
19 Jacola et al.		Structural MRI	Cross-sectional	__			

Table 1 (continued)

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
	Surgical resection and CRT (n = 50), Pre-CRT CT (n = 6)				IQ, working memory (behavioral measures), attention, executive function (parent ratings)	Parent reports of behavior and emotion regulation	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. Participants with infratentorial tumors had significantly greater mean NAWM volume than those with supertentorial 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.
20 Kesler et al.	Intrathecal CT	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 funtion and younger age at diagnosis were associated with functional hyperconnectivity.
21 Riggs et al.	CT, surgical resection, CSI	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 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.
22 Robinson et al.	Surgical resection (n = 17), CT and CRT (n = 5)	Task-based fMRI (letter N-back working memory)	Cross-sectional	—	Executive function, attention problems, IQ, working memory, processing speed	—	Survivors of pediatric brain tumors performed lower than controls on measures of general cognitive ability,

Table 1 (continued)

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
							attention, and executive function, and demonstrated altered brain activity during an fMRI working memory task. Survivors' neurocognitve 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.
23 Badr et al.	CT (n = 25), CT and 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 occuring in survivors who received cranial radiation, had diagnoses involving the CNS, or were classified as high-risk.
24 Genschaft et al.	CT	Structural MRI, DTI	Cross-sectional	Olfaction	Memory, executive function, attention, IQ	—	Relative to controls, the ALL group showed smaller gray matter volumes of the left hippocampus, amygdala, thalamus, nucleus accumbens, left calcarine gyrus, bilateral lingual gyri and the left precuneus. ALL survivors had lower hippocampus-dependent memory scores, and lower memory scores correlated with reduced hippocampal volumes. No evidence of white matter pathology was found.
25 Kuper et al.	Surgical resection	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.
26 Wolfe et al.	Surgical resection, CRT, and CT		Cross-sectional	—	IQ	—	Survivors of posterior fossa tumors showed typical activation patterns

Table 1 (continued)

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
		Task-based fMRI (letter N-back working memory)					(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.
27 Hosseini et al.	Intrathecal CT	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.
28 Zou et al.	CRT, CT, or both	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, innattention, 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 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.
29 Ashford et al.	CT	Structural MRI (at end of treatment)	Longitudinal	—	IQ, attention, working memory	—	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.
30 Ficek et al.	CT alone (n = 15), CT and CRT (n = 30)	Structural MRI and SPECT	Cross-sectional	—	—	—	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

Table 1 (continued)

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
							metabolite ratios in 29% (n = 13) of survivors and decreased mean NAA/Cr ratio in survivors who received CRT.
31 Kesler et al.	Intrathecal CT	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	—	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 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.
32 Robinson et al.	Intrathecal CT	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.
33 Aukema et al.	MB (n = 6): Surgical resection, CSI and CT. ALL: CT (n = 5 high-dose MTX, n = 6 low- dose MTX)	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 fasciliculus (IFO) and genu of the corpus callosum (gCC). Processing speed was 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.
			Longitudinal	—			

Table 1 (continued)

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
34 De Smet et al.	Surgical resection (n = 8), CT and CRT (n = 3), CRT (n = 1)	Structural MRI, SPECT			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-surgerical mutism was linked to perfusional deficits in supratentorial regions involved in language dynamics, syntax, naming, executive functioning, affective regulation, and behavior.
35 Reddick et al.	CT	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.
36 Carey et al.	CT only	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. 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.
37 Kirschen et al.	Surgical resection	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 hemispheral 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

Table 1 (continued)

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
							with controls. In patients, damage to the vermis and hemispheral lobule IV/V bilaterally was associated with decreased effects of articulatory suppression.
38 Zhang et al.	CRT and CT	Structural MRI	Cross-sectional	—	—	—	Brain tumor survivors showed reduced gray matter density in the thalamus and entorhinal cortex and reduced white matter density in the internal capsule, hypothalamus, corpus callosum, and cuneus of the occipital lobe, compared to healthy sibling controls.
39 Qiu et al.	Neurosurgery, CSI, CT	DTI	Cross-sectional	—	—	—	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.
40 Khong et al.	ALL: CT (n = 18), CT and CSI (n = 9) MB: Surgical resection, CSI, CT	DTI	Cross-sectional	—	IQ (full-scale, verbal, performance)	—	There were no significant differences in IQ scores across patient groups. Perecent 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.
41 Mabbott et al.	Surgical resection, CSR, 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 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.
42 Qiu et al.		DTI before the end of radiotherapy and at	Longitudinal	—	—	—	Across scans, increasing reduction in mean ΔFA over treatment for

Table 1 (continued)

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
	Surgical resection, CT, CSI + posterior fossa boost (total dose 56 Gy)	3 months, 6 months and 1 year after completion of radiotherapy.					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.
43 Reddick et al.	CT only (n = 84), CT and cranial irradiation (n = 28)	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 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.
44 Shan et al.	CRT	Structural MRI (at start of therapy and again 2 years later)	Longitudinal	—	—	—	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.
45 Konczak et al.	Surgical resection (n = 24); some also had CRT alone, CT alone, or CRT and CT	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),

Table 1 (continued)

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
							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 motor or cognitive recovery.
46 Reddickck et al.	Surgical resection and CSI (n = 52), adjuvant CT (n = 38)	Structural MRI	Longitudinal	—	—	—	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.
47 Reddick et al.	CT (IV-MXT)	Structural MRI (4 times throughout treatment)	Longitudinal	—	—	—	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.
48 Reddick et al.	CT (IV-MXT)	Structural MRI (4 times throughout treatment)	Longitudinal	—	—	—	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.
49 Zou et al.	Surgical resection (n = 16); CRT alone (n = 3), CT alone (n = 7), CRT 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

Table 1 (continued)

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
							for effects of quantitative differences in the BOLD responses of survivors as compared to healthy subjects.
50 Hill et al.	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.
51 Leung et al.	Surgical resection, whole brain irradiation, CT	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.
52 Mulhern et al.	Surgical resection 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. Greater attentional deficits were associated with reduced NAWM, particularly within the frontal lobe/prefrontal area and cingulate gyrus.
53 Nagel et al.	Neurosurgery, CRT, and CT	Structural MRI (mean num. scans per patient = 6, up to 5 years after treatment)	Longitudinal	—	—	—	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.
54 Chu et Al.	CT alone (n = 18), CT and CRT (n = 4), CT and whole-body irradiation (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.
55 Khong et al.	Surgical resection, CSI, CT	DTI	Cross-sectional	—	Intellectual outcome (school performance)	—	With the exception of frontal periventrical white matter, FA was significantly reduced in medulloblastoma patients compared to controls in all anatomical sites (including posterior fossa and supratentorial white matter).

Table 1 (continued)

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
							Decreased supratentorial white matter FA was associated with younger age at treatment, longer interval since treatment, and decline in school performance.
56 Pääkkö et al.	CT (n = 19), and CSI (n = 9)?	Perfusion MRI at end of treatment (n = 19), and SPECT (n = 17)	Cross-sectional	—	—	—	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.
57 Reddick et al.	Surgical resection (n = 40), whole–brain irradiation (n = 24), local irradiation only (n = 16), CT (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.
58 Palmer et al.	Neurosurgery, CSI, CT	Structural MRI (multiple times over 4-yr period)	Longitudinal	—	—	—	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 area were also observed in the genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium- with the greatest deviations from typical development occuring the isthmus and the splenium. These subregions of the corpus collosum, 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.
59 Mulhern et al.	Surgical resection and CRT (n = 42), CT (n = 29)	Structural MRI	Cross-sectional	—	IQ, verbal memory, and sustained attention	—	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

Table 1 (continued)

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
							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.
60 Levisohn et al.	Surgical resection	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 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.
61 Paakko et al.	CT (n = 33), CSI (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	—	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.
62 Reddick et al.	CSI (conventional or reduced dose) and CT	Structural MRI	Longitudinal	—	—	—	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
63 Mulhern et al.	MB: Surgical resection and CSI (n = 9), surgical resection, CSI and CT (n = 9), PF: surgery alone	Structural MRI (T1, T2, PD [proton density])	Cross-sectional	—	IQ (full-scale, verbal, performance)	—	Childhood MB survivors treated with cranial radiation (with or without CT) had significantly reduced 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.
64 Harila-Saari et al.	CT alone (n = 15), CT and CRT (n = 17)		Longitudinal	—		—	Overall, treatment-related brain abnormalities (e.g. high-intensity white

Table 1 (continued)

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
		Structural MRI (first at end of treatment, second 5 years later)			IQ, attention, language, motor/sensory/visuospatial function, memory		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.
65 Reddick et al.	Surgical resection, CRT 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 iraddiation alone. Patients who received surgery and irradiation demonstrated reduced white matter volumes relative to patients treated with surgery alone.

Abbreviations: ALL, acute lymphoblastic leukemia; PA, pilocytic astrocytoma; MB, medulloblastoma; PNET, primitive neuroectodermal tumor; WM, white matter; NAWM, normal appearing white mater; 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; ADC, apparent diffusion coefficient; CBF, cerebral blood flow.

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; Genschaft et al. 2013), which corresponded with poorer performance on hippocampal-dependent memory

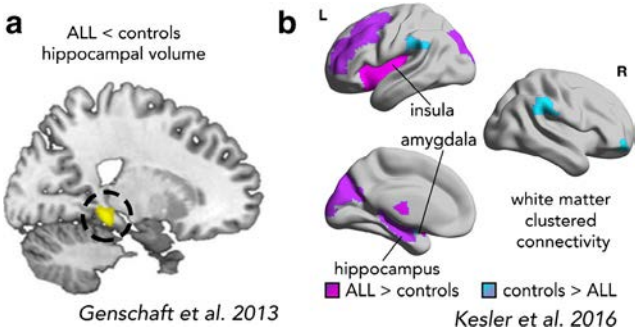

Fig. 2 Altered brain structure and function in young survivors of pediatric cancer. **a** Reduced hippocampal volume in n = 27 ALL survivors (ages 15-22 years; in remission for 6-18 years) treated with chemotherapy-only, relative to n = 27 matched controls (Genschaft et al. 2013). **b** Regional increases (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

tasks (Genschaft 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, Genschaft 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

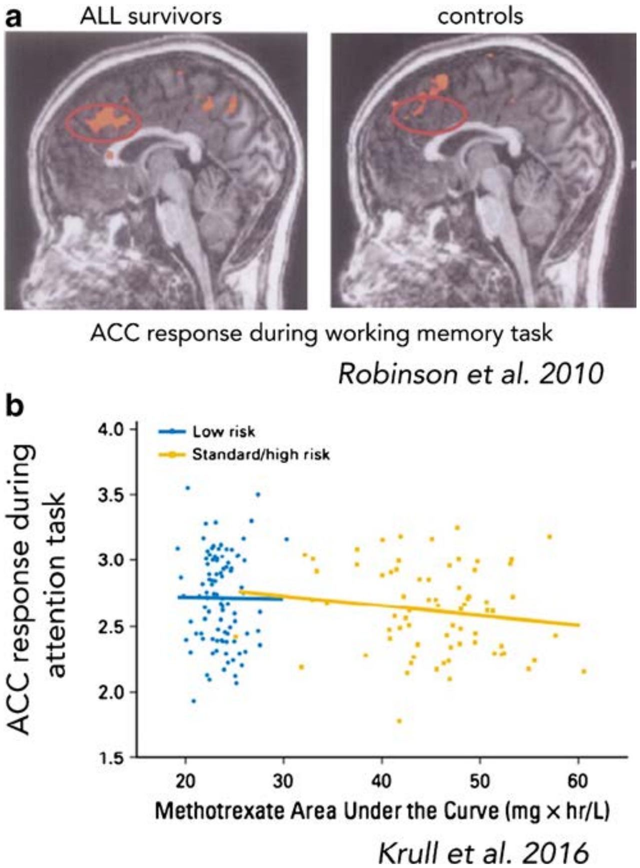

Fig. 3 Altered brain function in young survivors of pediatric cancer. **a** Significant increases in response in ACC, a core SEN region, in n = 8 young ALL survivors *(m* = 14.54 years, *SD* = 2.47; 4-12 years after treatment) relative to matched controls, during a working memory (n-back) paradigm (2-back 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

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 neuroprotective 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).

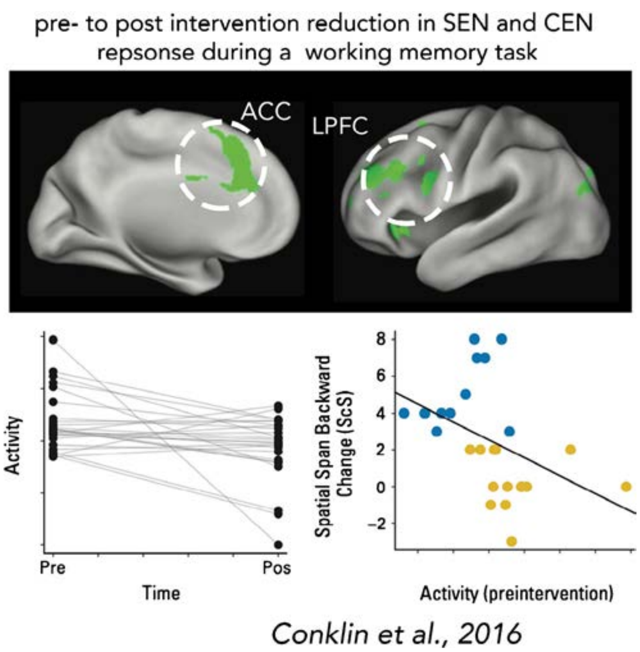

Fig. 4 Function of the salience and emotion network (SEN) and other large-scale neurocognitive networks represent key targets for psychosocial and behavioral interventions. 30 survivors of ALL or brain tumor who completed a 25-week computerized cognitive training intervention exhibited increased behavioral 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

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.

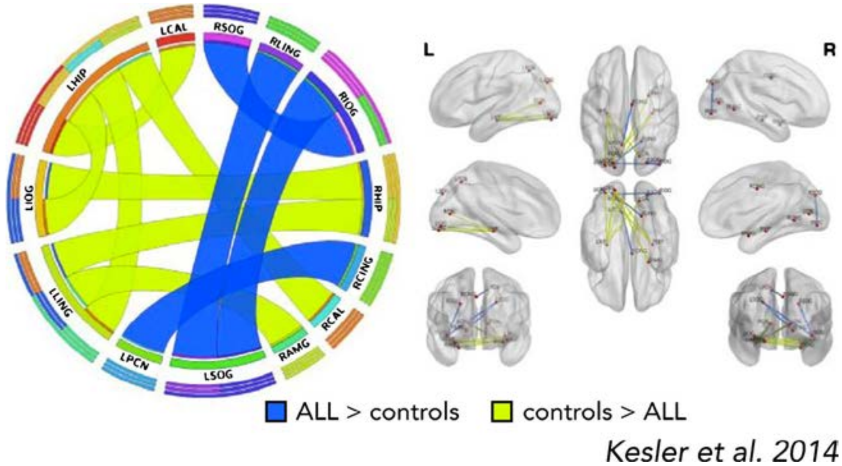

Fig. 5 Altered rsFC in young survivors of pediatric cancer. Regional increases (blue) and decreases (green-yellow) in rsFC in n = 15 young ALL (ages 8-15 years, 9-110 months off treatment) and n = 14 matched controls. In particular, ALL survivors showed reduced rsFC of amygdala ('RAMG') and hippocampus ('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

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

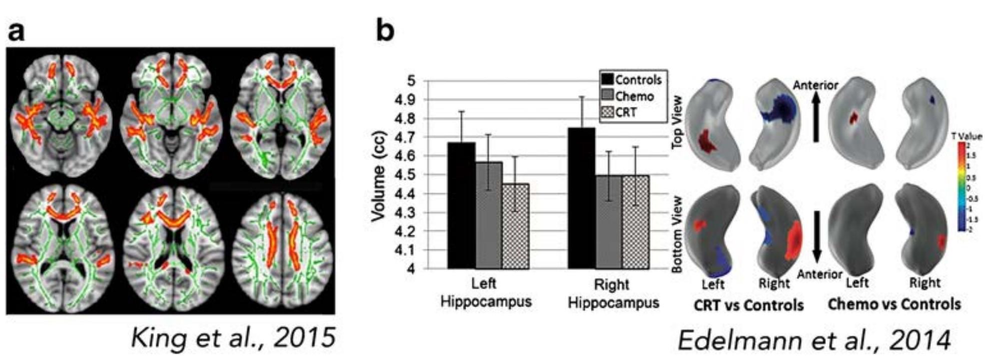

Fig. 6 Altered brain structure in adult survivors of pediatric cancer. **a** Relative to matched controls (n = 27), adult survivors of childhood brain tumor (n = 27, ages 18-32; average of 13.7 years [*SD* = 5.37] since diagnosis) demonstrate reductions in indicators of white matter integrity in frontal 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

Table 2 Review of neuroimaging studies in adult survivors of pediatric cancer

First author	Year of publicati on	Journal	Sample size (N)	Survivors (n)	Healthy controls (n)	Age at assessment (years)	Age at diagnosis in years (mean, SD, [range])	Time since diagnosis/ treatme nt in years (mean, SD,	Type of cancer
1 Chen et al.	2016	Neuroimage Clinical	32	16	16	22.5 (5.2) [1734]	7.6 (5.1)	14.9 (7.3)	Cerebellar tumor
2 Tamnes 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) [117]	15.38 (5.34) [524]	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) [1735]	7.65 (4.90) [117]	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) [117]	17.13 (5.43) [525]	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 pareital 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 [18.646.5]	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 [20.432.4], with dex: 24.6 [19.731.2]	Without dex: 8.7 [3.8-16.9], with dex: 11.8 [5.818.6]	Without dex: 15.9 [14.8-17.9], with dex: 13.3 [12.015.1]	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
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

Table 2 (continued)

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
14 Brinkman et al.	2012	Neuro-oncology	20	20	_	29 [21-36]	[2-17]	18 [12-25]	MB
15 Dellani 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	ALL

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 Tamnes 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, hippocampal and putamen volumes were significantly correlated with each other but not with total brain volume.
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	—	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 gyri) during a working memory task was

Table 2 (continued)

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
							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-occipitotemoral (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
8 Schuitema et al	CT (n=49), CT and CRT (n=44)	DTI	Cross-sectional	—	IQ, speed and accuracy of information processing, attention, working memory	—	Compared with controls, ALL and lymphoma survivors treated with CRT 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.
9 Zeller et al.	CT (n=130), CT and CRT (n=18), CT and stem-cell transplantation (n=3)	Structural MRI	Cross-sectional	—	IQ, processing speed, executive function, verbal learning/memory	—	ALL survivors showed smaller volumes of cortical gray matter, cerebral 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 effected 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
10 Edelmann et al.	CT (n=20 with prednisone and no dexamethasone, n=18 with dexamethasone)	Structural MRI, task-based fMRI (memory	Cross-sectional	—	IQ, academic performance, 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

Table 2 (continued)

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
		recognition tasks: word & face)					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.
11 Monje et al.	CT and CRT (n=10)	Structural MRI; task-based fMRI (memory encoding task)	Cross-sectional	—	Recognition memory	—	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.
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 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 funtion	—	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 intergrity 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

Table 2 (continued)

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
							brain volume and intracranial volume compared to controls. Concerning structural 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.
16 Porto et al.	CT (n=10), CT and CRT (n=10)	Structural MRI, DTI	Cross-sectional	—	—	—	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.

Abbreviations: ALL, acute lymphoblastic leukemia; PA, pilocytic astrocytoma; MB, medulloblastoma; PNET, primitive neuroectodermal tumor; WM, white matter; NAWM, normal appearing white mater; 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,

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

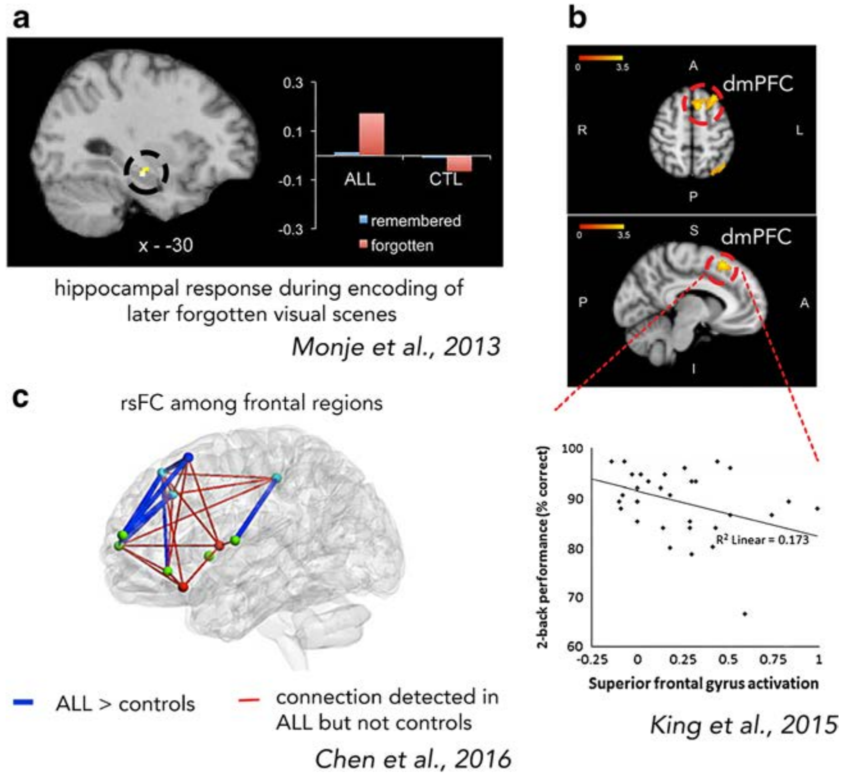

Fig. 7 Altered brain function in adult survivors of pediatric cancer. **a** Abnormal elevation in hippocampal activity during encoding of later forgotten items in n = 10 adult survivors of pediatric ALL (average age = 30.8 years; 20-30 years after treatment) relative to n = 10 matched controls ("CTL", 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

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

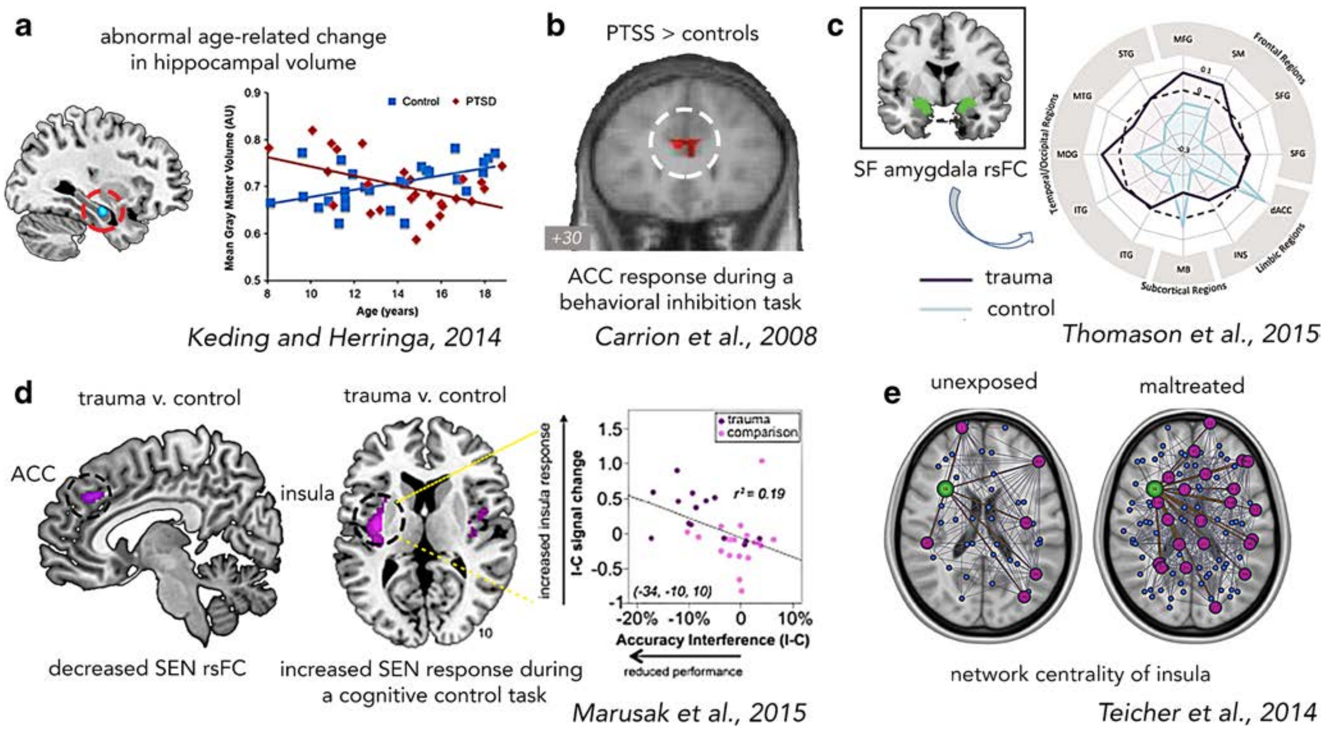

Fig. 8 Common alterations in brain structure and function in individuals exposed to more commonly-studied childhood experiences that involve similar elements of early threat (e.g., interpersonal violence, abuse), suggesting a role for neurotoxic effects of early threat exposure in neurodevelopmental 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-occiptal studies, involved in attention and visual processing (Thomason et al. 2015). **d** Relative to 19 matched controls, 14 youth exposed to interpersonal threat (*M* age = 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

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 sequela. 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 neurotropic 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 or 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 certainty 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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Martial Arts-Based Therapy Reduces Pain and Distress Among Children with Chronic Health Conditions and Their Siblings

Hilary A Marusak[1–3]
Allesandra S Iadipaolo[4]
Cindy Cohen[5]
Elimelech Goldberg[5,6]
Jeffrey W Taub[6,7]
Felicity WK Harper[3,7]
Martin H Bluth[5,8]
Christine A Rabinak[1,2,4,9]

[1]Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, MI, USA; [2]Merrill Palmer Skillman Institute, Wayne State University, Detroit, MI, USA; [3]Population Studies and Disparities Research Program, Karmanos Cancer Institute, Detroit, MI, USA; [4]Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA; [5]Kids Kicking Cancer, Southfield, MI, USA; [6]Department of Pediatrics, School of Medicine, Wayne State University, Detroit, MI, USA; [7]Department of Oncology, School of Medicine, Wayne State University, Detroit, MI, USA; [8]Department of Pathology, School of Medicine, Wayne State University, Detroit, MI, USA; [9]Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA

Objective: Test whether a martial arts-based therapy, Kids Kicking Cancer (KKC), can reduce pain and emotional distress in children with cancer, other chronic health conditions (e.g., sickle cell), and healthy siblings.

Methods: This study surveyed children's pain and distress levels immediately before and after a 1-hr in-person KKC class. Eligible participants were enrolled in standard KKC classes, were diagnosed with a chronic health condition (e.g., cancer, sickle cell) or were the sibling of a child diagnosed and were between the ages of 5–17 years (inclusive). Children reported on their pain and distress using Likert-style scales (Coloured Analog Scale and modified FACES scale, respectively). Friedman test was used to test for overall changes in pain and distress, and within subgroups. Age and sex effects were evaluated using Spearman's rank-order correlation. Additional Yes/No questions were administered regarding KKC satisfaction and use of techniques.

Results: Fifty-nine youth (19 cancer patients, 17 non-cancer patients, 23 siblings; 5–17 yrs, 26 females) completed this study. Overall, there was a significant reduction in pain (p = 0.033) and emotional distress ($p < 0.001$) after a 1-hr class, with 50% and 89% of youth reporting a reduction in pain and distress, respectively. On average, pain levels remained within the mild/moderate range on average (i.e., pre vs. post levels; pre: M = 1.67, post: M = 1.33) and emotional distress went from mild/moderate to none/mild distress, on average (pre: M = 1.92, post: M = 1.08). Youth with higher pre-class pain and distress reported greater reductions (p = 0.001 and $p < 0.001$, respectively). The reduction in pain appeared to be most pronounced with cancer and non-cancer patients. In contrast, the reduction in distress appeared to be most pronounced among healthy siblings. However, overall, reductions in pain and distress did not significantly differ among subgroups (i.e., cancer patients, non-cancer patients, siblings), and change in pain and distress was not associated with age or sex. Ninety-six percent of youth would recommend KKC to others and 81% reported using KKC techniques (e.g., the Breath Brake^{TM} or other martial arts techniques) outside of class, such as at home.

Conclusion: Results support the more widespread application of KKC as a psychosocial intervention for reducing pain and distress in various pediatric populations.

Keywords: meditation, mindfulness, oncology, psychosocial, sickle cell, leukemia

Correspondence: Hilary A Marusak
Tel +1 313-577-1278
Fax +1 313-577-6188
Email hmarusak@med.wayne.edu

Plain Language Summary

About one in four of children and adolescents in the United States have a chronic health condition, such as asthma, cancer, or diabetes. Childhood chronic health conditions and their associated treatments can be painful and emotionally distressing for children and their families,

and under or untreated pain or distress in childhood can negatively impact daily functioning and long-term outcomes. Siblings of children with chronic health conditions are also are at increased risk of experiencing pain and distress themselves. This study tested whether a martial arts-based therapy, Kids Kicking Cancer, can reduce pain and emotional distress in children with cancer, other chronic health conditions (e.g., sickle cell), and healthy siblings. The researchers found that a 1-hr Kids Kicking Cancer class reduces pain and emotional distress in children and 96% of children would recommend Kids Kicking Cancer to other children. Martial arts-based therapies such as Kids Kicking Cancer may be helpful for reducing pain and emotional distress among children with chronic health conditions and siblings.

Introduction

Globally, more than 300,000 children are diagnosed with cancer each year.[1] Another 300,000 children across the globe are born with severe hemoglobin disorders (e.g., sickle cell anemia) each year,[2] and many more live with other chronic- or life-threatening childhood health conditions, such as asthma, cystic fibrosis, hemophilia, and diabetes. The prevalence of chronic health conditions among children has increased over the past few decades,[3,4] and these conditions cause significant societal and individual burden.[5] Children with chronic health conditions and their families face enormous psychological stressors, which can disrupt daily life, impair social functioning and academic performance, and reduce overall quality of life for multiple family members.[6]

Childhood chronic health conditions and their associated treatments can be painful and emotionally distressing. Estimated rates of emotion-related psychological impairment (e.g., depression, anxiety, posttraumatic stress symptoms) among children with chronic illnesses range from 24% to 88%.[7–12] Children's distress reactions to treatment may cause difficulty in regulating pain, which many children with chronic illness experience at some point during the disease or its treatment.[13] Pain in the context of childhood chronic illness can be secondary to treatment procedures (e.g., bone marrow aspirations, intramuscular/intravenous injections), due to the disease itself (e.g., vaso-occlusive crisis), or side effects of treatment (e.g., postoperative pain, neuropathic pain).[13] Together, pain and emotional distress are prevalent among children with and without chronic health conditions and can negatively impact daily functioning and long-term outcomes.

Under or un-treated pain and distress during childhood and adolescence increases risk of later impairment. Studies show that as many as 73% of children and adolescents with chronic pain will continue to have pain in adulthood or develop new pain conditions.[14,15] Pediatric patients with chronic pain are also at an almost five times greater risk of lifetime anxiety disorder.[16] Pain and distress that lingers into adulthood is associated with disability, comorbid cognitive and emotion-related problems (e.g., anxiety, depression), and diminished work productivity.[17] Inadequate management of pain and emotional distress in childhood can lead to increased healthcare usage, reduced adherence to treatment procedures, morbidity, and even mortality. Further, pediatric chronic pain is associated with enormous economic burden, including an estimated $19.5 billion/year in the US due to healthcare costs, lost employment, and out-of-pocket expenses.[18] Thus, pediatric pain and emotional distress are significant public health concerns, throughout the lifespan.

Given the high prevalence and adverse effects of pediatric pain and emotional distress, there is a critical need for effective interventions. Existing evidence-based interventions for pediatric pain and distress include both pharmacological and non-pharmacological approaches, such as cognitive-behavioral approaches, mindfulness-based approaches, and medications (e.g., opioids, selective serotonin reuptake inhibitors [SSRIs]).[19,20] More comprehensive approaches that integrate both medical and psychosocial interventions may be more effective than usual care for reducing current pain and distress and reducing the risk of continued impairment into adulthood.[21] Compared to usual care, more comprehensive approaches to addressing pediatric pain and address can also reduce healthcare costs. For example, such integrated treatment programs have been shown to save an estimated US $27,199/year per family,[22] and free up physician time to see 42% more patients, generating an additional US$1142/day in revenue in pediatric clinics.[23] However, access to evidence-based psychosocial support for children with chronic health conditions throughout the disease trajectory (e.g., diagnosis through survivorship) is limited.[24]

Kids Kicking Cancer (KKC, https://kidskickingcancer.org) is an international organization that provides martial arts-based therapy for children with cancer, other chronic illnesses, as well as, healthy siblings, as a part of the "Heroes Circle" program. Now embedded in more than 90 children's hospitals and other locations in seven countries (US, Italy, Israel, Canada, South Africa, Zambia, Zimbabwe), KKC provides psychosocial support, social interaction, procedure preparation, and sibling support – which are specific areas of need highlighted by the Standards for Psychosocial Care for Children with Cancer and their Families.[24] KKC uses martial arts-based techniques including meditations, breathing, and specific empowering movements to help children learn to cope with the pain and distress of their disease and/or its treatment. Such mindfulness-based approaches have been previously shown to be effective for reducing pain and improving mental health among children and adolescents.[20,25] However, KKC is unique in that it is a martial arts-based therapy that pairs meditation and mindfulness approaches with physical movement and themes of purpose and empowerment, which may have additional benefit.[26,27]

Another unique aspect of KKC is that programming includes healthy siblings who, although often part of the healthcare management of the patient, are increasingly recognized as a psychologically at-risk group themselves.[28,29] Research shows that siblings of children with chronic pain are at increased risk of experiencing pain themselves, as compared to their non-sibling peers.[30] Further, research on siblings of children with cancer indicate that a significant subset experience posttraumatic stress symptoms, negative emotional reactions (e.g., fear, worry, sadness, anger), and poor quality of life.[28] Siblings may also experience pain or distress vicariously,[31] as a result of seeing their brother or sister in pain or distress, or distress associated with bereavement.[32] Pain and emotional distress are also prevalent among non-sibling, nonclinical populations. Approximately one-quarter to one-third of children and adolescents experience chronic pain (e.g., headache, abdominal pain)[33] and about one-third of youth are affected by an anxiety disorder.[34] Given the increased risk of poor psychosocial adjustment, prior research has highlighted the need for interventions that include siblings of children with chronic illness.[35]

We previously reported that a 1-hr KKC session can reduce pain among children with cancer, with 85.3% reporting a reduction in pain.[27] Using an independent sample, the present study aims to extend this prior important work to children with other chronic health conditions, as well as, healthy siblings – populations that can experience significant pain and emotional distress. We also extend the prior study by measuring emotional distress, in addition to pain.

Method

Participants

This study reports on 59 children and adolescents, ages 5–17 years (median = 10.37 years; 26 females). Eligible participants were enrolled in a standard KKC class, were diagnosed with a chronic childhood health condition or were a sibling, and were between the ages of 5–17 (inclusive). Children younger than age 5 were excluded to enhance reliability of pain and distress ratings. Classes were held at the KKC Southfield, Michigan location (Metro Detroit) and thus outside of the hospital setting. The majority of participants at the KKC Southfield location are recruited through healthcare providers (e.g., social workers, oncologists) at the Children's Hospital of Michigan (Detroit, Michigan), or from word-of-mouth. Sixty-one percent (n = 36) of participants were patients, and the remaining 39% were siblings (n = 23). Of the children who were patients, 52.8% (n = 19) had cancer diagnoses, including acute lymphoblastic leukemia (ALL), neuroblastoma, and brain tumor (see Table 1). Seventeen children had non-cancer chronic illnesses, such as sickle cell, hemophilia, asthma, chronic pain, and diabetes. Overall demographic data, and demographic data by subgroup (i.e., cancer patients, non-cancer patients, healthy siblings), are given in Table 1. Age and sex distribution did not differ between cancer and non-cancer patients, or among the three subgroups (i.e., cancer patients, non-cancer patients, healthy siblings; $p > 0.05$). This study was carried out as a secondary analysis of collected data for the internal evaluation of KKC programming. Data were therefore limited with regard to how many siblings were related to patients in this sample, details of individual participant recruitment, detailed medical history (e.g., treatment type, dosage), and current patient status (e.g., active treatment, survivorship). All data accessed complied with relevant data protection and privacy regulations and were maintained with confidentiality. The study procedures were approved by the Wayne State University Institutional Review Board.

Kids Kicking Cancer Classes

KKC classes usually include a mix of children with cancer, non-cancer chronic health conditions, and healthy siblings. Classes are taught by specially trained black belt-level martial arts therapists, and its mantra is "Power, Peace, Purpose", which is intended to imbue the participant with self-control, awareness, and a feeling of empowerment. Classes also provide a unique platform for students to interact with peers undergoing similar experiences and allow students to learn and share how martial arts techniques can be used to overcome daily challenges (e.g., disease-related or other daily stressors). For example, the KKC "Ninja Needle" technique was developed to help

Table 1 Participant Demographics

Overall (N = 59)	**n**	**%**
Sex		
Female	26	44.1
Male	33	55.9
Subgroup		
Cancer patients	19	32%
Non-cancer patients	17	29%
Healthy siblings	23	39%
	M	SD
Age (years)	10.1	2.8
Cancer Patients (n = 19)	**n**	**%**
Sex		
Female	7	37%
Male	12	63%
Diagnosis		
Acute lymphoblastic leukemia	11	30.6
Brain tumor	2	5.6
Neuroblastoma	2	5.6
Neurofibromatosis	1	2.8
Osteosarcoma	1	2.8
Rhabdomyosarcoma	1	2.8
Not specified	1	2.8
	M	SD
Age (years)	10.6	2.7
Non-Cancer Patients (n = 17)	**n**	**%**
Sex		
Female	9	53%
Male	8	47%
Diagnosis	17	47.2
Sickle cell	7	19.4
Hemophilia	4	11.1
Pain clinic	1	2.8
Asthma	1	2.8
Diabetes	1	2.8
Chiari Malformation	1	2.8
Other hematological disorder	1	2.8
Nephrotic syndrome	1	2.8
	M	SD
Age (years)	10.7	2.8
Healthy Siblings (n = 23)	**n**	**%**
Sex		
Female	10	56.5
Male	13	43.5
	M	SD
Age (years)	9.1	2.9

children cope with needle-related procedures, such as venipunctures. KKC martial arts therapists are also integrated into several hospital systems and provide bedside support and interventions to help children cope with treatment-related procedures in real-time.

A standard KKC class begins with the mantra "Power. Peace. Purpose." and is followed by a deep breathing exercise (Breath Brake™), consisting of breathing in, holding the breath and breathing out at 3 to 4 second intervals each and an introspective body-scan led by specially trained martial arts therapists. A series of moving meditations are then taught, including kicks and punches, and movements are tailored based on physical abilities and clinical indications of the child. There is no physical contact (e.g., sparring) during sessions. During the class, the martial arts therapists may also teach certain specific techniques, e.g., the Ninja Needle technique for needle-related medical procedures, depending on class experience. Instructors also ask students how they used KKC techniques in their daily lives, for example, use of the Breath Brake™ at home, school, or during treatment-related procedures. For more information on KKC techniques and standard class formats, see Bluth et al.[27]

Procedure

Participants prospectively reported on their pain and distress before and after a standard KKC class session, using brief surveys. Participants were assisted in completing these brief surveys by specially trained KKC martial arts therapists, staff, and/or volunteers. Surveys consisted of standardized Likert scales of pain and emotional distress (explained to children as "bad", "worried", or "anxious"). Pain was measured using the Coloured Analog Scale[36] on a scale from 0 to 10 (where 0 is no pain and 10 is the worst possible pain). Distress was rated using an adapted version of the FACES scale (see[37,38]) on a scale from 1 to 5 (where 1 is no distress and 5 is the worst possible distress). Following the class, students were also asked if they: (1) would recommend KKC to other children (yes/no), (2) felt like a powerful martial artist (yes/no), (3) practiced or used the Breath Brake™ at least once over the past week (yes/no), and (4) practiced or used other martial arts techniques at least once over the past week (yes/no). Students were asked whether or not they felt like a powerful martial artist given that the mantra of KKC is Power. Peace. Purpose., and students are taught to reframe themselves as a powerful martial artist who can face any life challenge rather than a victim of their experience. Power emanates from introducing an expanded element of control of one's situation. The mind–body movements coalesce to move the individual from passive acceptance of one's predicament to active engagement toward change. Peace derives from acceptance of one's current situation and can mitigate negative feelings that often create behavioral stagnation. Purpose introduces elements of conviction and positive value for one's existence and situation. It can help to transcend one's situation and transform benign activity into something greater than the sum of its parts.

Data Analysis

Responses on the pain and distress Likert scales showed positive skew, with only 11.2% of responses exceeding 2 for pain levels and only 12% of responses exceeding 2 for distress. To reduce the skew in the data, we recoded the data to increase the frequency within response categories by collapsing across categories. In particular, pain and distress scores were recoded as follows: 0 = no pain or distress, 1 = mild pain or distress, 2 = moderate pain or distress, and 3 = severe pain or distress. Of note, post-class pain level was missing from one participant (hemophilia patient), and post-class distress rating was missing from one participant (cancer patient).

Analyses were first performed across the entire sample (i.e., overall; N = 59), and then within the largest subgroups separately: (1) cancer patients, (2) non-cancer patients, and (3) healthy siblings. We included siblings in the overall analysis given that siblings are also at increased risk of pain and emotional distress.[28,39,40] First, we quantified the number of children who reported pre-class pain or emotional distress (i.e., scores > 0). Next, for those who reported pre-class pain or distress (>0), we quantified the number of children who reported an increase, decrease, or no change in pain or distress over the course of the 1-hr class session. Then, to test whether observed changes reached statistical significance, we used non-parametric Friedman's two-way analysis of variance by ranks to compare pain and distress scores reported before vs. after class. All results were considered significant at a $p < 0.05$ (two-tailed) threshold and utilized the recoded data. Spearman's rank-order correlation was used to test whether pre-class pain or distress was correlated with the change score (pre-post) in pain or distress. Spearman's rank-order correlation was also used to test whether age and sex were associated with levels of pre-class pain or distress or change (pre-post) in pain or distress. Statistical analyses were performed in SPSS Software version 26 (IBM Corporation). For the additional questions regarding KKC satisfaction and use of techniques, "Yes" and "No" responses to each question were quantified across the entire sample, and for each subgroup separately (i.e., cancer patients, non-cancer patients, healthy siblings).

Results

Pain

Overall

Across all children, 41% reported at least some pain (i.e., scores > 0) before the class session. Age and sex were not associated with pre-class pain ($p > 0.05$). Of the children who reported no pre-class pain (n = 34), three (9%) reported mild pain at the post-class time point (1 cancer patient, 1 non-cancer patient, and 1 sibling). Overall, for those reporting pre-session pain (>0), 50% of children reported a reduction in pain, 37% reported no change in pain, and 8% reported an increase in pain. See Figure 1A for distribution of pre- and post-class pain, by group. For those who reported pre-class pain, there was a significant reduction in pain (i.e., pre vs. post levels; pre: M = 1.67, post: M = 1.33, $\chi^2(1) = 4.57$, $p = 0.033$) and pain levels remained within the mild/moderate range on average (Figure 2). Change in pain scores (i.e., pre-post) did not significantly differ by group (cancer patients, non-cancer patients, siblings; $p > 0.2$). For those reporting pre-class pain, age and sex were not associated with change in pain scores (i.e., pre-post; $r_s = -0.03$, $p = 0.82$ and $r_s = 0.12$, $p = 0.38$, respectively). Higher pre-class pain, was however, associated with a greater reduction in pain ($r_s = 0.42$, $p = 0.001$).

Cancer Patients

Pre-session pain (>0) was reported by 42% of cancer patients. For cancer patients who reported pre-session pain, 37% reported a reduction in pain, 63% reported no change in pain, and no cancer patients reported in increase in pain. Pre- and post-class pain levels were M = 1.69 and M = 1.31, respectively, among cancer patients, $\chi^2(1) = 3$, $p = 0.08$.

Non-Cancer Patients

Pre-session pain (>0) was reported by 53% of non-cancer patients. For non-cancer patients who reported pre-session pain, 78% reported a reduction in pain, 22% reported no change in pain, and no non-cancer patients reported in increase in pain. The overall reduction in pain appeared to be most pronounced among non-cancer patients, with

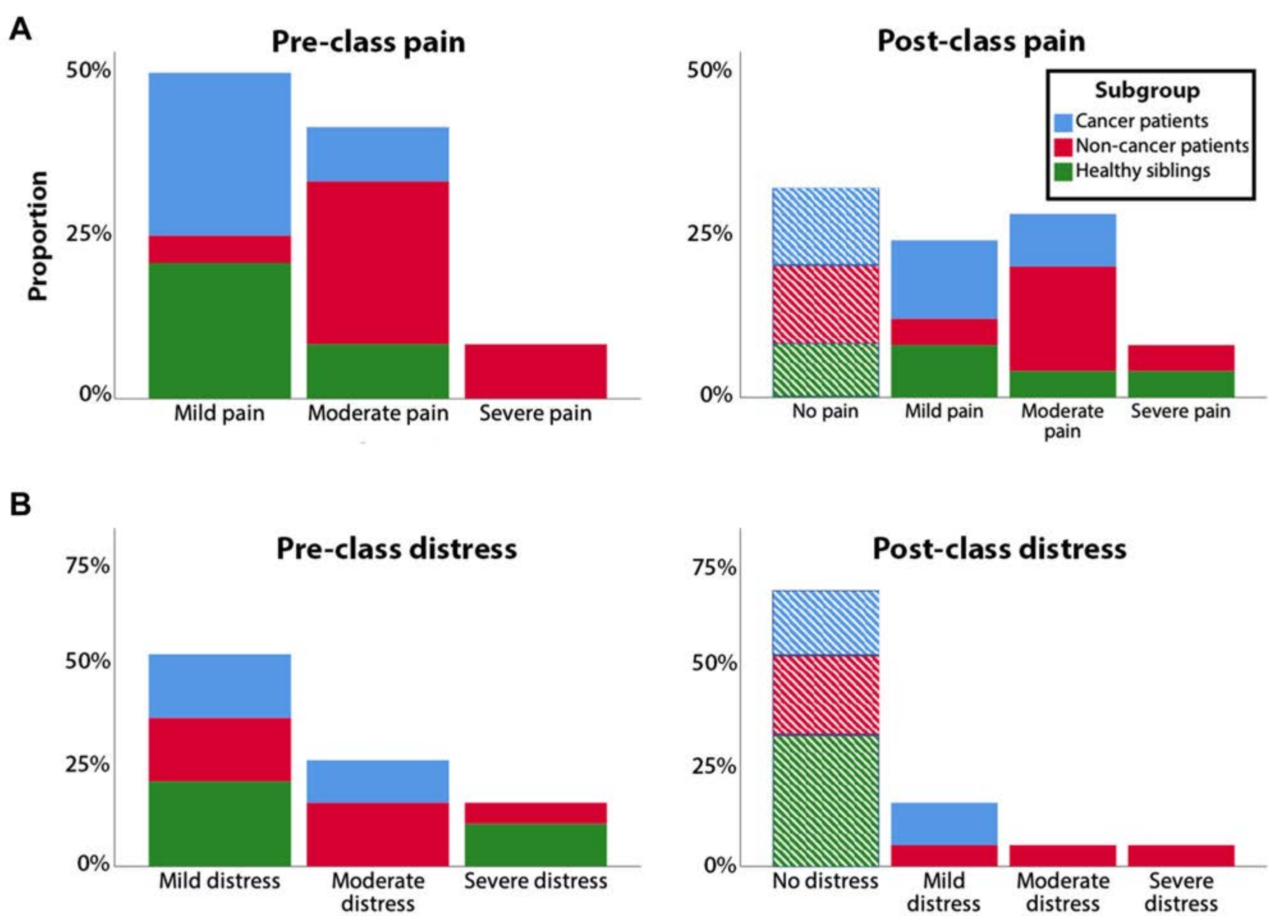

Figure 1 Distribution of pre- and post-class pain (**A**) and emotional distress (**B**), by group. Top row (panel (**A**)) indicates pre- and post-class pain. Bottom row (panel (**B**)) indicates pre- and post-class distress. The vertical axis indicates the portion of participants who reported pain or distress in each category. Only participants are shown who reported pre-class pain or distress (>0; N = 24 for pain, N = 18 for distress). Dashed bars indicate participants who reported no post-class pain or distress. Of note, post-class pain rating was missing for one participant (hemophilia patient), and post-class distress rating was missing for one participant (cancer patient).

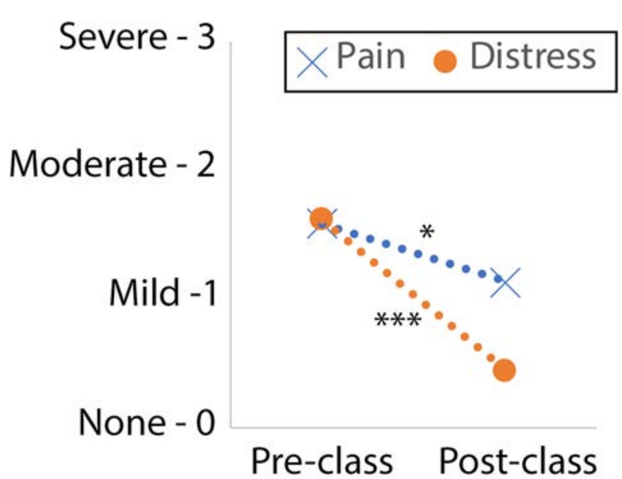

Figure 2 Significant reduction in pain and distress over the course of one class. Overall average of pre- and post-class pain and emotional distress. *p < 0.05, ***p < 0.001.

pre- and post-class pain levels of M = 1.78 and M = 1.22, respectively, $\chi^2(1) = 3.57$, $p = 0.06$.

Siblings

Pre-session pain (>0) was reported by 30% of healthy siblings. For siblings who reported pre-session pain, 33% reported a reduction in pain, 33% reported no change in pain, and 33% reported in increase in pain. Pre- and post-class pain levels did not differ among healthy siblings (pre: M = 1.5, post: M = 1.5).

Emotional Distress

Overall

Across all children, 31% reported at least some distress (i.e., scores > 0) before the class session. Age and sex were not associated with pre-class distress (p > 0.05). Of the children who reported no pre-class distress (n = 34), two (6%) reported mild distress at the post-class time point (1 cancer patient, 1 sibling). Overall, for those reporting pre-session distress (>0), 89% of children reported a reduction in distress, 6% reported no change in distress, and 6% reported an increase in distress. See Figure 1B for distribution of pre- and post-class distress, by group. For those who reported pre-class distress, there was a significant reduction in distress (i.e., pre vs. post levels; pre: M = 1.92, post: M = 1.08, $\chi^2(1) = 13.24$, $p < 0.001$), and went from mild/moderate distress to none/mild distress (Figure 2). The change in distress scores (i.e., pre-post) did not significantly differ by group (cancer patients, non-cancer patients, siblings; $p > 0.7$). For those reporting pre-class distress, age and sex were not associated with change in distress scores (i.e., pre-post; $r_s = 0.057$, $p = 0.68$ and $r_s = -0.11$, $p = 0.43$, respectively). Higher pre-class distress, was however, associated with a greater reduction in distress ($r_s = 0.78$, $p < 0.001$).

Cancer Patients

Pre-session distress (>0) was reported by 26% of cancer patients. For cancer patients who reported pre-session distress, 80% reported a reduction in distress, 20% reported no change in distress, and no cancer patients reported in increase in distress. Pre- and post-class distress was M = 1.9 and M = 1.1, respectively, among cancer patients, $\chi^2(1) = 4$, $p = 0.046$.

Non-Cancer Patients

Pre-session distress (>0) was reported by 41% of non-cancer patients. For non-cancer patients who reported pre-session distress, 86% reported a reduction in distress, no non-cancer patients reported no change in distress, and 14% reported in increase in distress. Pre- and post-class distress was M = 1.86 and M = 1.14, respectively, among non-cancer patients, $\chi^2(1) = 3.57$, $p = 0.06$.

Siblings

Pre-session distress (>0) was reported by 26% of healthy siblings. For siblings who reported pre-session distress, 100% reported a reduction in distress. The overall reduction in distress appeared to be most pronounced among healthy siblings, with pre- and post-class distress ratings of M = 2 and M = 1, respectively, $\chi^2(1) = 6$, $p = 0.014$.

Satisfaction and Use of KKC Techniques

Overall, 96% of children responded "Yes" to the Yes/No question "Would you recommend KKC to other children?" and 82% responded "Yes" to the Yes/No question "Do you feel like a powerful martial artist?". Further, 81% reported using the Breath Brake^{TM} at least once over the past week, and 76% reported using martial arts techniques at least once outside of class over the past week. Distribution of yes/no responses for each question did not significantly differ by age, sex, or subgroup ($p > 0.05$).

Discussion

These results demonstrate that martial arts-based therapy may be an effective psychosocial intervention for reducing pain and emotional distress among children with cancer, non-cancer chronic childhood health conditions (e.g., sickle cell, diabetes), and healthy siblings. Overall, 50% and 89% of children reported a reduction in pain and emotional distress, respectively, after a 1-hr KKC class. Although change in pain or distress scores did not significantly differ among subgroups (cancer patients, non-cancer patients, siblings), pre-class pain was more prevalent among cancer and non-cancer patient subgroups relative to siblings, and accordingly, the reduction in pain appeared to be more pronounced among cancer and non-cancer patients as compared to siblings. Although pre-class emotional distress was common across subgroups (i.e., cancer patients, non-cancer patients, siblings), the reduction in emotional distress appeared to be most pronounced among siblings. The reduction in emotional distress among siblings is important because siblings are increasingly recognized as a psychologically at-risk group.[28] Importantly, the KKC program was highly agreeable among children, with 96% reporting that they would recommend KKC to other children. Eighty-two percent reported feeling like a martial artist and 81% reported that they used the Breath Brake^{TM}[27] outside of class, suggesting that these techniques may be helpful for coping with every day and disease-related stressors. Change in pain or emotional distress and satisfaction with KKC did not differ by age, sex, or subgroup. Taken together, these data add to the growing evidence base supporting the use of martial arts-based therapy for the management of pediatric pain and distress.[27]

More than half (59%) of patients in the present sample reported a reduction in pain over the course of a 1-hr KKC class session. The proportion reporting a reduction in pain was lower than observed in our previous study in pediatric cancer patients,[27] with 85% reporting a reduction in pain. Although detailed medical history (e.g., treatment type, dosage) and current status (e.g., active treatment, survivorship) was not collected in this study, the different rates may be due to heterogeneity in patient age, disease state, and/or treatment history. In particular, the age range of the present sample was 5–17 years whereas our prior study (Bluth et al[27]) was 3–19 years. Importantly, in our prior study,[27] the greatest reduction in pediatric cancer pain was reported among older youth (e.g., 15–19 years) whereas there was a relatively limited number of older children (i.e., only two children were ≥ 15 years) in the present sample. In addition, in both studies, pain was measured outside of the hospital setting and thus we did not anticipate a large number of children in acute pain. Future research should test whether KKC martial arts techniques are effective at reducing pain and distress during treatment-related procedures (e.g., port-starts). KKC martial arts therapists are already integrated into approximately 90 hospital and/or healthcare-related systems across the globe and provide bedside support and interventions to help children cope with treatment-related procedures in real-time. For example, martial arts therapists guide children through breathing and meditation exercises (e.g., the Breath Brake^{TM}) during treatment procedures, including the specialized KKC "Ninja Needle" technique which was developed to help children cope with needle-related procedures. Larger prospective studies are needed to examine the longer-term effects of single versus multiple sessions, and of various disease states and indications.

Children with chronic health conditions often experience fear, emotional distress, and worry regarding death, feelings of separation from their friends and family, and recurring social confinement in the hospital.[41] Distress can contribute to anxiety, depression, and posttraumatic stress symptoms.[42] Fear, anxiety, and emotional distress in these pediatric populations can lead to a range of poor outcomes, including avoidance of subsequent medical monitoring,[43] reduced adherence to treatments, poorer quality of life,[44] and increased pain sensitivity.[45] Emotional distress can also exacerbate medical-related adverse events, such as precipitation of vaso-occlusive crisis in sickle cell disease.[46] Our data suggest that a 1-hr KKC session can reduce emotional distress among children with cancer, other chronic childhood health conditions, as well as, healthy siblings. Future research should examine whether there are longer-term benefits of KKC participation (i.e., beyond a single session) and whether the observed reductions in pain and distress are clinically meaningful. However, preliminary results from a school-based martial arts KKC program suggest that positive effects of martial arts training are sustained over five months post-intervention (Marusak et al, under review).

Notably, children who reported higher pre-class pain and/or distress showed greater reductions over the course of the 1-hr KKC class. These results are consistent with those reported by Bluth et al[27] and suggest a potential indication (e.g., high pain or distress ratings) for referral to KKC by social workers or other psychosocial support staff (e.g., Child Life Specialists). Nonetheless, children who are not experiencing acute pain or distress may also benefit from learning martial arts under the KKC program or other venues, as these techniques can help them cope with everyday challenges, including stressors associated with medical-related treatments, school, peers, or home life. Children may also benefit from the opportunity to interact with peers who are going through similar experiences, as prior research indicates that social relationships predict better adjustment to pediatric cancer.[47] Importantly, across both studies, there was no effect of sex on reductions in pain, and in this study, distress. The present study also adds that change in pain or emotional distress and satisfaction with KKC does not differ by sex or subgroup. Taken together, these results replicate and extend our prior work by including a wider range of pediatric populations (non-cancer patients, healthy siblings) and an assessment of emotional distress.

The observed significant reduction in emotional distress among healthy siblings is important because siblings are often not included in psychosocial care; yet, siblings frequently experience distress related to the sick child's wellbeing, changes in family dynamics and daily routines, feelings of social exclusion, and even rivalry for parental attention.[48] Among childhood cancer families, siblings report lower quality of life and higher rates of anxiety, depression, and social withdrawal as compared to non-sibling controls.[49] Consistent with these data, about a quarter of siblings reported pre-class emotional distress in this study. Martial arts techniques may be beneficial for helping siblings to cope with stressors associated with having a child with chronic illness in the family, as well as, with everyday stressors (e.g., schoolwork, peer and family conflicts). Inclusion of siblings together with patients in KKC classes may promote adjustment of the entire family, as social support, family togetherness, and family cohesion have been shown to predict better adjustment among both pediatric patients and siblings.[49,50]

Almost one-third of siblings in the present study reported pre-class pain. This is consistent with prior studies[51–53] reporting that 15–35% of children in a nonclinical population experience persistent or chronic pain (e.g., headache, neck and shoulder pain, abdominal pain). One recent survey study of over 1000 children and adolescents (ages 8–18 yrs) found that 60% reported pain within the past three months, and that higher pain was associated with lower health-related quality of life.[54] Together, these findings suggest that pain problems are common and can have negative impacts on life (e.g., mood, relationships, school functioning), even in a nonclinical population. Siblings of children with a chronic pain or chronic health conditions may be at an even higher risk of developing a pain condition themselves. For example, a subset of healthy siblings of children with functional abdominal pain also report abdominal pain and overall,[30] siblings of children with chronic health conditions are at greater risk of developing somatic symptoms (e.g., headaches, fatigue) as compared to their peers.[39,40] Siblings may also have vicarious experiences of contagious and empathetic pain,[31] or experience pain and distress associated with bereavement.[32] Together, these findings are consistent with a growing body research showing that a sibling's experience of pain or illness can affect children's functioning in several domains, including emotional, family, social, and school difficulties.[28]

Study Limitations

Child self-reports of pain and distress can be unreliable. However, children were assisted in filling out the surveys and child-friendly language was used (e.g., "bad", "worried", "anxious"). In addition, we selected measures that have been validated for use in children ages 5+.[36–38] Although we examined effects of age, sex, and subgroup on changes in pain and distress, the study design and relatively limited sample size precluded further exploration of additional predictive variables (e.g., particular diagnoses, treatments, disease stage). This study was not designed as a randomized controlled trial, but rather was a secondary analysis of prospective data collected as a part of an internal program evaluation. Larger prospective studies are needed to identify baseline factors that predict greater response to KKC, and to test longer-term effects. Similarly, larger "dismantling" studies are needed to identify the most effective therapeutic components of the KKC class (e.g., social interaction, Breath Brake™) against a control arm (e.g., waitlist).

The relatively limited sample size of subgroups and heterogeneity in terms of age and diagnosis restricted our ability to test for factors that may predict response to martial arts-based therapy. We attempted to examine the impact of this variability by testing for effects of age and testing for overall effects, and effects within our largest subgroups (i.e., cancer, non-cancer patients). Nonetheless, it is encouraging that, despite this heterogeneity, we found an overall reduction in pain and emotional distress following a 1-hr martial arts-based session, which suggests that martial arts-based therapy may be applicable to a wider range of pediatric populations. These observed significant effects may be even stronger in a larger sample size, particularly within a more homogeneous sample (e.g., ALL or sickle cell patients). This requires further study.

Another consideration is that KKC classes were not conducted in conjunction with medical-related procedures (e.g., bone marrow aspiration), and thus, many children reported little to no pain and/or distress prior to class. Nonetheless, for children who did report pre-class pain and/or distress, we observed significant reductions over the course of a 1-hr session. Many children with chronic health conditions do experience daily pain related to the disease itself, or side effects of treatment (e.g., nerve pain, mouth sores, neuropathic pain). The observation that a KKC intervention reduced pain and distress in siblings of children with chronic disease is compelling. Research by Deavin et al[55] has demonstrated that siblings of children with chronic disease may have a suppression of their needs and reduced communication, which highlights the need for approaches to deal with such changes in family dynamics. To this end, KKC's beneficial effect many have important application to the wellbeing of the entire family unit. Future studies should assess whether the observed analgesic and anxiolytic effects of KKC are similarly observed or more pronounced during medical-related procedures for patients and the arborizing effect on siblings and other family members.

Conclusion

Together, the results of the present study suggest that martial arts-based therapy is effective for addressing the critical problem of pain and emotional distress among children with cancer, other chronic health conditions, and healthy siblings. Results support the more widespread application of KKC to a range of pediatric populations, including every day and medical-related stressors, including vaccinations and pediatric intensive care unit visits.

Abbreviations

KKC, Kids Kicking Cancer; ALL, acute lymphoblastic leukemia.

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Disclosure

The authors declare no conflicts of interest.

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A Virtual Reality Meditative Intervention Modulates Pain and the Pain Neuromatrix in Patients with Opioid Use Disorder

Mohammed M. Faraj,* Nina M. Lipanski,† Austin Morales,‡ Elimelech Goldberg,*,§ Martin H. Bluth, MD, PhD,*,§,|||| Hilary A. Marusak, PhD,‡,¶ and Mark K. Greenwald, PhD‡,||

*School of Medicine, Wayne State University, Detroit, Michigan; †Department of Biological Sciences, University of California, San Diego; ‡Department of Psychiatry and Behavioral Neurosciences, Wayne State University; §Kids Kicking Cancer; ¶Merrill Palmer Skillman Institute for Child and Family Development, Wayne State University; ||Department of Pharmacy Practice, Wayne State University; ||||Maimonides Medical Center, Brooklyn, New York, USA

Correspondenceto: Mark K. Greenwald, PhD, Department of Psychiatry and Behavioral Neurosciences, Tolan Park Medical Building, 3901 Chrysler Service Drive, Suite 2A, Detroit, MI 48201, USA. Tel: +1 313 993 3965; Fax: +1 313 993 1372; E-mail: mgreen@med.wayne.edu.

Conflicts of interest: E.G. is founder and global director of Kids Kicking Cancer (KKC), a nonprofit organization that developed this martial arts intervention. M.B. is the global medical director of KKC. H.A.M. has received previous grant funding from KKC, and this research was funded by a subcontract from KKC (E.G.) to M.K.G. There are no other conflicts of interest to report.

Abstract

Objective. Standard of care for opioid use disorder (OUD) includes medication and counseling. However, there is an unmet need for complementary approaches to treat OUD patients coping with pain; furthermore, few studies have probed neurobiological features of pain or its management during OUD treatment. This preliminary study examines neurobiological and behavioral effects of a virtual reality-based meditative intervention in patients undergoing methadone maintenance treatment (MMT). **Design.** Prospective, non-blinded, single-arm, 12-week intervention with standardized assessments. **Setting.** Academic research laboratory affiliated with an on-site MMT clinic. **Methods.** Fifteen (11 female) MMT patients completed a virtual reality, therapist-guided meditative intervention that included breathing and relaxation exercisessessions were scheduled twice weekly. Assessments included functional magnetic resonance imaging (fMRI) of pain neuromatrix activation and connectivity (pre- and post-intervention), saliva cortisol and C-reactive protein (CRP) at baseline and weeks 4, 8 and 12; and self-reported pain and affective symptoms before and after each intervention session. **Results.** After each intervention session (relative to pre-session), ratings of pain, opioid craving, anxiety and depression (but not anger) decreased. Saliva cortisol (but not CRP) levels decreased from pre- to post-session. From pre- to post-intervention fMRI assessments, pain task-related left postcentral gyrus (PCG) activation decreased. At baseline, PCG showed positive connectivity with other regions of the pain neuromatrix, but this pattern changed post-intervention. **Conclusions.** These preliminary findings demonstrate feasibility, therapeutic promise, and brain basis of a meditative intervention for OUD patients undergoing MMT.

Key Words: Methadone; Meditation; fMRI; Pain Neuromatrix; Postcentral Gyrus; Craving; Cortisol

Introduction

Opioid misuse, overdose, and opioid use disorder (OUD) constitute a public health emergency that is persistent [1] and projected to escalate [2]. In 2018, about 2 million individuals in the US had an OUD [3], which is associated with a high mortality rate (±130 daily deaths in the US), comorbid psychiatric disorders (e.g., anxiety), and other poor health outcomes [4]. Further interventions are needed to reduce the impact of opioid misuse, OUD, and overdose.

Chronic pain affects >100 million individuals in the United States and opioids prescribed to treat pain can increase risks of misuse, physiological dependence, and OUD [5]. Previous research indicates 64.4% of OUD patients report chronic pain [6], which may occasion relapse [7], reduce adherence to OUD treatment, and reduce quality of life [8]. Additionally, prevalence of OUD among patients with chronic pain is 34.9% [9]. Standard of care for OUD includes medication, such as methadone maintenance therapy (MMT), and counseling. Given adverse effects of chronic pain among patients with OUD, there is an unmet need for complementary approaches to assist OUD patients with pain.

One potential complementary approach for reducing pain in OUD is mindfulness-based therapies (e.g., breathing, meditation). Mindfulness is the practice of focusing on the present moment to improve control over one's own sensations, feelings, and thoughts. Mindfulness approaches have been shown to reduce pain intensity and pain-related psychological consequences, and to improve functional status and quality of life [10]. Findings from studies in healthy populations suggest that meditative interventions can mitigate pain, independent of the endogenous opioid system [11, 12]. Previous controlled studies report that mindfulness meditation can reduce self-reported pain in patients with chronic pain conditions [13] and in opioid-using chronic pain patients [14].

Although meditation-based therapies show promise for reducing pain in individuals with OUD and other groups, neurobiological mechanisms underlying these analgesic effects remain unclear. The "pain neuromatrix" is a core set of brain regions recruited when an individual experiences physical pain [15]. The pain neuromatrix includes primary nociceptive processing regions including the thalamus, anterior insula, caudate, postcentral gyrus (PCG), anterior midcingulate cortex (aMCC), and posterior cingulate cortex (PCC). The pain neuromatrix also includes regions involved in sensory/affective appraisal, for example, dorsolateral prefrontal cortex [16, 17], polymodal regions that are not specifically related to nociception such as the ACC, and primary and secondary somatosensory cortices [18]. Relevant to the present study, regions of the pain neuromatrix are engaged when one person watches another person experiencing physical pain [19]. Importantly, meditation has been shown to modulate activity and connectivity within the pain neuromatrix [20]. Prior studies reported lower prefrontal activation and higher insula and PCG activation to pain-related processing following a meditation intervention [21, 22]. The pain neuromatrix has also been implicated in the development and maintenance of OUD [4]. Thus, interventions that target the pain neuromatrix may be beneficial for addressing mechanisms involved in pain and OUD etiology.

This pilot study examined neurobiological and behavioral effects of a novel meditative intervention in OUD patients undergoing MMT. We hypothesized that participation in this meditative intervention would lead to less task-induced activation and resting-state connectivity of the pain neuromatrix; lower saliva levels of cortisol (index of hypothalamic-pituitary-adrenal [HPA] axis response) and C-reactive protein ([CRP], inflammatory biomarker); and less self-reported pain, opioid craving, and affective symptoms.

Methods

Setting

We recruited participants enrolled in an urban, academic-affiliated MMT program. This not-for-profit, evidence-based practice, treatment research-oriented clinic (unique in the Detroit metropolitan catchment area) had a census of about 150 patients at the time of this study. Services are primarily funded by Medicaid or Block grants. The majority of patients in this clinic are African American, have comorbid medical and psychiatric conditions, and report prior (often multiple) OUD treatment episodes. Most patients in this clinic are maintained on methadone, and a few on buprenorphine.

Participants

Participants were enrolled and completed the study from October 8, 2018, through September 20, 2019. All participants were ≥18 years old, met criteria for OUD, and were stabilized on their methadone dose for >1 month before screening. We excluded individuals who were pregnant or lactating, had a current severe Axis I psychiatric disorder (e.g., psychosis, bipolar), past-year suicidal ideation/attempt, and contraindications to the intervention (e.g., cognitive or physical disability, unwillingness to undergo the procedures) or magnetic resonance imaging (MRI). Demographic and substance use history data were obtained from patients' clinical charts. All participants provided informed consent following approvals from Wayne State University and State of Michigan IRBs. The study was registered at ClinicalTrials.gov (NCT03595007).

Study Design

This pilot study was a single-arm, 12-week virtual reality (VR) meditative intervention. Upon enrollment, we obtained pre-intervention baseline measures of chronic pain, affective distress (i.e., anxiety, depression), emotion regulation and self-efficacy. Intervention sessions were scheduled twice weekly on methadone clinic attendance days. Before and after each session, participants rated their pain and other symptom severity using visual analog scales (VASs). Saliva samples were collected before and after four sessions (baseline and weeks 4, 8, and 12). Two MRI scans were performed, before (baseline) and after the 12-week intervention, to measure pain neuromatrix activity and connectivity. Participants were compensated for completing research visits using electronic payments.

Pre-Intervention Baseline Measures

Chronic pain severity and functional interference was measured using the Brief Pain Inventory (BPI) [23], which has been validated in MMT patients [24] Participants also completed the Beck Depression Inventory-II (BDI-II) [25, 26], which measures past 2-week depression symptoms; State-Trait Anxiety Inventory (STAI) [27], which differentiates state anxiety from more chronic trait anxiety; Distress Tolerance Scale [28], which measures the ability to remain drug abstinent in the face of difficulties [29, 30]; Perceived Stress Scale [31], which measures the degree to which the subject views past-month situations in his/her life as stressful; Difficulties with Emotion Regulation Scale [32], which measures non-acceptance of emotional responses, difficulties in engaging in goal-directed behavior, impulse control difficulties, lack of emotional awareness, limited access to emotion regulation strategies, and lack of emotional clarity; and Alcohol and Drug Use Self-Efficacy Scale [33], which assesses self-efficacy and responses to high-risk situations that can precipitate substance use. Items are grouped into negative affect, social positive withdrawal/urges, and physical/other concerns; subjects indicate how "tempted" and "confident" they would be in each situation, yielding two scores.

Virtual reality Meditative Intervention

Meditative interventions, including martial arts, yoga, and mindfulness-based approaches, are a promising approach for attenuating pain [34]. Martial arts, in particular, as a therapeutic model leverages the popular notion that associates martial artists as being powerful. This is an attractive theme to children diagnosed with, and being treated for, life-threatening illness [35, 36]. It may also resonate with patients exhibiting diminished self-regulation and perceived loss of self-agency including substance use disorders [37]. Although hundreds of martial arts styles are taught worldwide (e.g., Tai Chi, Chi Gung, Karate), limb movements, controlled breathing and mental focus (e.g., meditation) are unifying factors. The approach described here differs from other modalities of meditation, mindfulness, and fighting-oriented martial arts, as it blends key elements from such modalities, uses VR, and is individually tailored [35, 36].

Using narration and VR technology to teach and engage the participant, the intervention coordinates physical (arms, hands, upper body) movements with a specific breathing technique, and meditative exercises (which are neither distracting nor dissociative) to vividly imagine and act as a powerful martial arts "warrior" who must face down his/her internal personal struggles. The physical movement/breathing sequence uses the Breath Brake®, which involves three cycles of inhaling (3-second duration) while hands are raised, palms up from waist to shoulders, breath-holding (3-second duration) while hands are rotated to palms facing down, and exhaling (3-second duration) while palms are lowered from shoulders to waist, each time envisioning "breathing in the light and breathing out the darkness." This breathing process is accompanied by upward body movement during inhalation, lowering the body while relaxing muscles during exhalation, toward propagating a gentle, fluid wavelike motion throughout the cycle. At the end of exhalation, the participant forcefully expels the breath, which engages vagal responses shown beneficial in many disease states [38, 39]. This motor sequence decouples the automatic breathing rhythm into distinct quanta, and is intended to promote active engagement and control, in contrast to being passively receptive in conventional therapy.

The 12-week intervention consisted of 30-min sessions scheduled twice-weekly. Participants completed 16–24 sessions ($M = 21.7$, $SD = 2.1$). Sessions occurred in a private, soundproof room. The trained therapist worked 1:1 with the participant to teach VR-assisted martial arts-based movements, breathing and meditative techniques. Participants learned the Kids Kicking Cancer (KKC; www.kidskickingcancer.org) mantra "Power. Peace. Purpose." and practiced the Breath Brake® [35, 36] as described above. The VR platform used a Windows Mixed Reality headset attached to a gaming laptop with an advanced processor and video card that assured a seamless 360' immersive audio and video experience. During sessions, the therapist first asked the participant to recount past-week events, whether they used the Breath Brake® or other techniques for stressful life events, and reminded them to use the Breath Brake® the next time a stressful event arose. The participant then underwent a 15-minute VR-guided meditation. The first meditation introduces the KKC program, presented with eight KKC children. Author EG explains to the participant that the children have less pain when they know others are learning from them. The participant is put in the position of helping children with cancer by doing the Breath Brake®, and that the therapist will report their progress to the children. The next scene takes place with the children as avatars teaching the participant how to do a Breath Brake®. The children also inform the participant that the greatest opponent to any martial artist lies within oneself. The children explain that parts of our brains can turn into a beast that can seek to destroy us. In the next scene the participant is brought back, through the optic nerve into his/her brain, to face the beast. The limbic system twirls and turns into a beast, which demands the participant get rid of the children. "You love me. I am everything to you." The child appears next to the beast and reminds the participant to use his/her breath to destroy the beast. "Your beast is a liar," the child informs the participant. As the participant breathes in, the VR fills with a powerful light. As the participant exhales, he/she can see his/her breath as smoke that makes holes in the beast. The beast begins to shrink. The beast is fully washed away in the next section during a waterfall meditation. The participant is warned the beast will return but that when we continue to use our light to defeat it, the beast will no longer have the power to destroy us. Participants were also issued a mobile phone-based application for their own use at home. Using the voice of a child cancer patient in the KKC program, the software issued reminders to the participant, encouraging him/her to take Breath Brakes® at scheduled intervals (default was every 2 hours, but this could be adjusted by the participant).

VAS ratings

Before and after each intervention session, the participant rated his/her momentary level of "pain," "opioid craving," "anxiety," "anger," and "depression" using a VAS (0–10; 0 = not at all; 10 = extremely).

Saliva Samples

At pre-intervention baseline and weeks 4, 8, and 12, pre- and post-session saliva samples were collected using a non-stimulated, passive drool method, collected with a salivette held under the tongue for 3 min. Samples were frozen at −20° C prior to analysis.

MRI Scanning

Scan Parameters

MRI data were collected before and after the 12-week intervention using a single Siemens 3 T MAGNETOM Verio system (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. BOLD fMRI data were acquired using a multi-echo T2*-weighted, multiband-accelerated EPI sequence with 51 near-axial 64 × 65 slices (voxel size 2.9-mm isotropic; TR = 1500-ms; TEs = 15, 31, 46-ms; flip angle = 83, FOV = 186 × 186; GRAPPA factor = 2, multi-band factor = 2). High-resolution structural (anatomical) images were acquired each session using a T1-weighted MP-RAGE sequence (voxel size: 0.7 × 0.7 × 1.3-mm; TR = 1680-ms; TE = 3.51-ms; flip angle = 9; FOV = 256 × 256; 128 slices; 1.34-mm slice thickness).

Functional Tasks

During fMRI scans, participants completed a 10-minute resting-state task. They were instructed to remain still with eyes closed during a functional localizer task that reliably isolates neural activity in the pain neuromatrix without inducing physical pain [19]. This task involves passively viewing a 5-minute 36-second video clip from the animated short film "Partly Cloudy" (Pixar Animation Studios). The movie clip includes events that evoke mental states and physical sensations of characters, including the character undergoing a physically painful event (e.g., electrocuted by an electric eel). In addition to pain-related events, other movie events were coded as non-pain conditions: control (e.g., no character-related events), social (characters interacting), and mentalizing (e.g., viewer is led to think about the character's thoughts, such as when a character falsely believes he has been abandoned by his companion). Due to technical problems, post-intervention data were missing for two participants for the pain task and for two participants for the resting-state task.

Data analysis

VAS Scores

To account for missing data, VAS responses (pain, opioid craving, anxiety, anger, depression) were averaged across protocol weeks to create four bins (i.e., weeks 1–3, 4–6, 7–9, 10–12), separately for pre- and post-session scores. Parallel session (pre/post) × bin repeated-measures ANOVAs were conducted for each VAS score in IBM SPSS v.26. Follow-up *t*-tests were conducted following significant main effects or interactions, and all results were considered significant at $P < .05$ (two-tailed). Greenhouse-Geisser correction was used for sphericity violations.

Cortisol and C-Reactive Protein (CRP)

Saliva samples were analyzed by Salimetrics LLC (State College, PA) using radioimmunoassays for cortisol and CRP levels. To reduce skewness of distributions, raw cortisol and CR *P* values were $\log_{10}$ transformed prior to parallel session (pre/post) × week (baseline and weeks 4, 8, 12) repeated-measures ANOVAs in SPSS. Follow-up *t*-tests were conducted following significant main effects or interactions, and all results were considered significant at $P < .05$ (two-tailed).

fMRI Preprocessing

Preprocessing and denoising steps were performed for BOLD fMRI data (pain neuromatrix task, resting-state task) using multi-echo independent components analysis (ME-ICA) software (v.2.5; https://github.com/ME-ICA/me-ica) [40]. ME-ICA leverages quantitative T2* decay measures to separate BOLD from non-BOLD (e.g., head motion) signals using ICA. This step circumvents relatively arbitrary preprocessing steps and reduces signal dropout by acquiring an early echo (15-ms) and optimal combination of echoes. Multi-echo imaging can increase signal-to-noise ratio and fMRI effect sizes compared to standard denoising approaches, which is useful for pilot studies [41]. Preprocessing steps in ME-ICA include coregistration to anatomical images and normalization to Montreal Neurologic Institute (MNI) standard space. FMRI scan quality was assessed using framewise displacement (FD), a measure of frame-to-frame movement [42]. Mean FD in the unprocessed data for the pain neuromatrix task was 0.37 mm (SD = 0.25) at baseline and 0.45 mm (SD = 0.3) at post-intervention. For the resting-state task, raw mean FD was 0.33 mm (SD = 0.23) at baseline, and 0.4 mm (SD = 0.26) at post-intervention. ME-ICA preprocessing and denoising for task and resting-state data significantly reduced head motion compared to the raw data ($ts > 10$, $ps < 0.001$).

Pain Neuromatrix Task

The optimally combined and denoised task BOLD fMRI time-series data sets were submitted to Statistical Parametric Mapping software (SPM8; https://www.fil.ion.ucl.ac.uk/spm/software/spm8/) for analysis. Data were modeled using a general linear model (GLM), following prior work [19]. First-level models included condition regressors associated with the four event types in the movie (pain, control, social, and mentalizing). These events were modeled as boxcar functions and convolved with a canonical hemodynamic response function.

Pain neuromatrix activation was isolated using the contrast, pain > mentalizing. Group-level analyses were conducted using complementary region-of-interest (ROI) and whole-brain exploratory approaches. ROI and whole-brain analyses both used well-established approaches to correct for multiple tests (i.e., GLM across all brain voxels). The ROI approach restricts the search space to a priori ROIs implicated in neural processes of interest (here, pain-related processing), then controls for multiple comparisons within that search space by extracting single-value summary measures (e.g., weighted mean neural activation; 40]. The whole-brain approach applied cluster correction, a common correction method in fMRI analyses, which relies on the fact that voxels are not completely independent [43]. This approach controls familywise error (FWE) rate. We also used Monte Carlo simulations to identify a minimum cluster size (i.e., minimum number of contiguous voxels that are significant) at a conservative voxel-wise threshold ($P < 0.001$), following prior recommendations [43].

For the ROI approach, we analyzed five pain neuromatrix ROIs from Jacoby et al. [19] using the same task in healthy individuals and the same contrast. We created spherical ROIs (12-mm radii) centered on peak activation (pain > mentalizing) for the aMCC, right and left anterior insula (AI), right and left PCG (Figure 1). For each participant, we extracted and analyzed from baseline and post-intervention scans the first principal component of the pain > mentalizing activation in each ROI (β-estimates). First, we conducted one-sample *t*-tests to evaluate whether activation in each ROI significantly differed from 0 at baseline and post-intervention scans, separately. Then, we applied paired-sample *t*-tests to assess activation change in each ROI between baseline and post-intervention. Pearson bivariate correlations were applied to test whether baseline pain severity or functional interference (BPI), modulated pain-related activity in pain neuromatrix ROIs at baseline or post-intervention. Exploratory correlations were conducted to examine whether saliva cortisol or CRP levels were related to pain-related neuromatrix activation. Within SPM8, a complementary whole-brain FWE corrected threshold $pFWE < 0.05$ was applied for exploratory purposes, to evaluate overall patterns of pain-related activation separately at baseline and post-intervention (one-sample *t*-tests), and for changes in activation between baseline and post-intervention (paired-samples *t*-tests). The whole-brain corrected threshold was determined using AFNI's (version AFNI_19.2.24: linux_openmp_64) 3dFWHMx (compile date: September 14, 2019, https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dFWHMx.html) and 3dClustSim (voxelwise $P < .001$; cluster threshold = 5 voxels). This approach accurately models the spatial autocorrelation inherent in fMRI data [44]. All xyz coordinates provided in this report are in MNI convention.

Resting-State Connectivity

We also examined resting-state functional connectivity of the pain neuromatrix. Resting-state functional connectivity is based on measurement of spontaneous fluctuations in fMRI signals and is commonly used to probe stable patterns of brain network organization at rest, or independent of task-specific constraints. Prior research demonstrates that resting-state connectivity patterns correspond highly with brain activation and connectivity patterns observed during tasks [45–47], are reliable across contexts (e.g., at rest or across various tasks; 45], vary between neurotypical and abnormal individuals, and correspond with measures of chronic pain or acute pain sensitivity [48, 49]. These findings suggest resting-state patterns reflect underlying synaptic efficacies in brain networks and thus correspond to a canonical or "intrinsic" state of functional brain organization [50]. Here, we focused on resting-state connectivity of pain neuromatrix ROIs that showed significant pain-task activation, that is, left and right PCG (see *Results*). These analyses were performed using multi-echo independent components regression (ME-ICR) [40]. Rather than using the optimally combined BOLD time series, ME-ICR uses the independent BOLD components derived from ME-ICA as the effective degrees of freedom for each subject to control for false positives [40]. BOLD components were submitted to the MATLAB-based program CONN software v.19.c [51] for seed-based connectivity of left and right PCG ROIs using Pearson bivariate correlation. The correlation was calculated between the extracted vector of weights for each ROI and every other brain voxel. Fisher's r-to-Z transform was then applied to the resulting correlation image. At the group level, we first performed one-sample *t*-tests to examine patterns of connectivity for left and right PCG at baseline and post-intervention. Next, paired-sample *t*-tests were used to examine changes in left and right PCG connectivity between baseline and post-intervention. Finally, regression was used to test whether baseline pain severity or functional interference was associated with left and right PCG connectivity at baseline or post-intervention, or change in connectivity between baseline and post-intervention. Results were considered significant using a whole-brain corrected threshold determined using 3dFWHMx and 3dClustSim (voxelwise $P < .001$; cluster

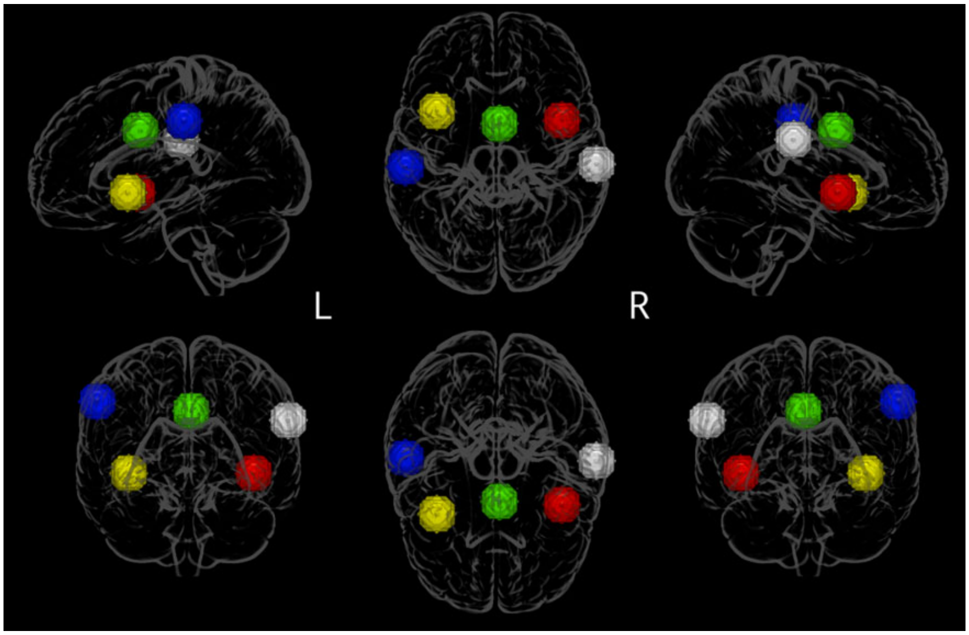

Figure 1. Pain neuromatrix regions of interest (ROIs) from Jacoby et al. (2016). Left = sagittal view; right: coronal view from front. Red: right anterior insula; yellow: left anterior insula; green: anterior middle cingulate cortex; white: right postcentral gyrus; blue: left postcentral gyrus. ROIs defined using 12 mm spheres around pain neuromatrix peaks reported in Jacoby et al. (2016).

threshold = 5 voxels). Resulting test statistics are given as Z-scores, which refers to the z statistic at the peak coordinate location. For baseline connectivity patterns, the Z-score was computed from the *t*- and *P* values derived from the group-level one-sample *t*-test. Higher Z-scores represent stronger connectivity between brain regions. For pre-post changes in connectivity, the Z-score was computed from the *t*- and *P* values derived from the group-level paired-samples *t*-test. Higher Z-scores represent greater pre-post intervention changes in functional connectivity between regions.

Results

Baseline Characteristics

Fifteen participants completed the study (Table 1). The sample was primarily female, balanced on race and injection drug use; several participants had co-occurring substance use or mental health problems. Participants were chronic opioid users (primarily heroin) and were receiving an average methadone dose of about 95 mg at entry into the study.

Baseline pain severity ranged from 0 to 32, and baseline pain functional interference ranged from 0 to 59 (Table 1). Location of the most severe chronic pain varied across participants; however, most patients (93.3%) reported low-back pain. Maximum pain in the past 24-hr was 4.8 of 10 (SD = 3.8), with 10 being "the most extreme pain imaginable". BPI pain severity and functional interference scores were positively correlated, $r(15)=0.69$, $P = .004$, but not associated with age, sex, race, years of education, state anxiety or depression scores, methadone dose during the intervention (max, min, average, modal), nor baseline scores for Alcohol and Drug Use Self-Efficacy, or Difficulties in Emotion Regulation, $ps>0.05$.

Session and Week-Related Changes in VAS Scores

Session (pre/post) × week (binned) repeated-measures ANOVA demonstrated a significant main effect of session for VAS pain scores: post-session levels were lower than pre-session levels ($F(1, 42)=5.04$, $P = .042$, $\eta p^2=0.265$; Figure 2A). There was also a significant main effect of session on opioid craving, anxiety, and depression scores: post-session levels were lower than pre-session levels ($ps<0.05$). For craving, there was also an effect of week, $F(1.85, 25.84)=4.59$, $P = .022$, such that craving decreased from weeks 1–6, increased from weeks 7–9, and decreased again from weeks 10–12 ($ps<0.05$). There were no significant main effects or interactions for anger ($ps>0.05$).

Session and Week-Related Changes in Salivary Cortisol and CRP

Session (pre/post) × week repeated-measures ANOVA for saliva cortisol and CRP showed a significant main effect of session on cortisol, $F(1, 14)=22.69$, $P < .001$, $\eta p^2=0.62$ (Figure 2B). Post-session cortisol levels were lower than pre-session. There were no significant main effects or interactions for CRP ($ps>0.05$).

Table 1. Participant demographic characteristics and substance use history (n = 15)

Variable	n	%
Sex		
Female	11	73
Male	4	27
Age		
19–29 years	2	13.33
30–49 years	5	33.33
50+ years	8	53.33
Race		
White	8	53.3
Black	7	46.7
Disabled	2	13.3
Injection opioid use	7	46.7
Marital status		
Single/widowed/divorced	11	73.3
Married or cohabitating	4	26.7
Unemployed	13	86.7
Comorbid substance use disorder	8	53.3
Cocaine	5	33.3
Benzodiazepines	2	13.3
Comorbid current mental health diagnosis	7	46.7
Major depressive disorder	5	33.3
Anxiety disorder	2	13.3
	M	SD
Average methadone dose (mg)	94.9	30.6
Years of opioid use	22.6	16.4
Years of education	11.4	1.6
Pain severity (BPI)	15.2	10.0
Pain functional interference (BPI)	20.9	19.5
State anxiety (STAI-S; range, 0–80)	49.3	2.7
Depression symptoms (BDI-II; range, 0–63)	12.5	10.1
Distress tolerance (DTS; range, 0–75)	58.7	11.1
Perceived stress (PSS; range, 0–40)	23.2	6.2
Difficulties with emotion regulation (DERS; range, 0–180)	82.1	10.6
Alcohol and drug use self-efficacy (ADUSE); tempted (range, 0–50)	39.7	19.4
Alcohol and drug use self-efficacy (ADUSE); confident (range, 0–50)	71.5	25.2
Baseline pain (VAS; range, 0–10)	6.6	2.4
Baseline opioid craving (VAS; range, 0–10)	5.2	1.3
Baseline anxiety (VAS; range, 0–10)	8.2	2.6
Baseline anger (VAS; range, 0–10)	3.8	0.8
Baseline depression (VAS; range, 0–10)	4.0	1.13

Pain severity and functional interference measured using the Brief Pain Inventory (BPI); state anxiety measured using the State-Trait Anxiety Inventory (STAI-S); depressive symptoms measured using the Beck Depression Inventory-II (BDI-II); VAS, visual analog scale. DTS data missing for one participant; PSS data missing for two participants.

Pain Neuromatrix Activation

At baseline, left and right PCG showed significantly positive activation, $t(14)=4.69$, $P < .001$, and $t(14)=2.88$, $P = .012$, respectively (Figure 3A). No other ROIs showed activation that significantly differed from zero at baseline or post-intervention ($ps>0.05$). Activity in left PCG significantly decreased from baseline to post-intervention, $t(12)=2.61$, $P = .023$ (Figure 3B). No other ROIs showed a significant change in activation from baseline to post-intervention ($ps>0.05$). No regions showed significant activation at baseline or post-intervention, or

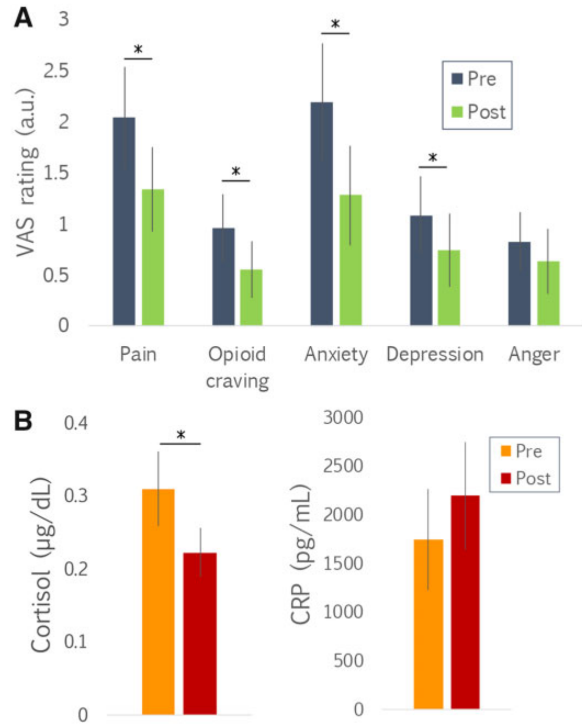

Figure 2. (A) Significant pre-post session reductions in self-ratings of pain, opioid craving, anxiety, and depression. **(B)** Significant pre-post session reduction in salivary cortisol. Raw values for cortisol and C-reactive protein (CRP) are given but analyses performed on $\log_{10}$ transformed values. $*P < .05$.

between baseline and post-intervention, at the exploratory corrected whole-brain threshold $pFWE<0.05$.

Higher baseline pain functional interference was associated with higher pain-related activation only in left PCG at baseline, $r(15)=0.56$, $P = .03$ (Figure 3C). Pain severity was not associated with activation in any ROI at baseline or post-intervention.

We also conducted exploratory correlation analyses to examine whether saliva biomarkers were related to task activation. Higher baseline pre-session cortisol was associated with higher pain-related activation in left PCG at baseline, $r(15)=0.591$, $P = .02$. Higher baseline pre- and post-session cortisol levels were associated with higher pain-related activation in right and left AI at post-intervention ($rs = 0.56–0.7$, $ps<0.05$). Higher baseline pre-session CRP was associated with higher pain-related activation in left PCG at baseline, $r(14)=0.557$, $P = .037$, and higher baseline post-session CRP was associated with higher pain-related activation in the right PCG ($r(12)=0.652$, $P = .021$) and left AI ($r(12)=0.640$, $P = .025$) at post-intervention. However, none of the above results survived correction for multiple comparisons.

Pain Neuromatrix Functional Connectivity

At baseline, PCG was positively connected with other pain neuromatrix regions including dorsal posterior insula, inferior frontal gyrus, precentral gyrus, middle frontal gyrus, superior temporal gyrus, inferior parietal

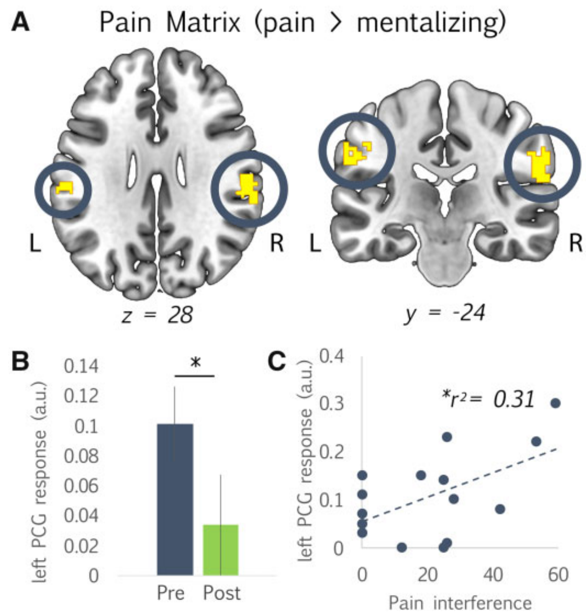

Figure 3. (A) Activation in the left and right postcentral gyrus (PCG) regions of interest (ROIs) during the Partly Cloudy task for the contrast pain > mentalizing during pre-intervention baseline. Image thresholded at $P < .05$ uncorrected, masked within the five pain neuromatrix ROIs (see Figure 1) for display purposes. **(B)** Reduction in pain-related activity in the left PCG at post-intervention, compared to pre-intervention baseline (contrast: pain > mentalizing), $*P < .05$. **(C)** Higher self-reported pain functional interference at baseline is associated with higher pain-related activation in the left PCG (contrast: pain > mentalizing) at baseline.

lobe, and cerebellum (Table 2). At baseline, PCG showed negative connectivity with posterior cingulate cortex (PCC) and with clusters in the superior temporal gyrus and middle frontal gyrus that differed from those with positive connectivity. These patterns are consistent with prior studies showing positive connectivity between the PCG and other regions of the pain neuromatrix at rest and during noxious stimulation (e.g., [48, 49]).

Next, we examined changes in PCG connectivity between baseline and post-intervention (Table 2). PCG and other pain neuromatrix regions exhibited lower connectivity strength (in terms of magnitude and spatial extent) at post-intervention compared to baseline, including the superior temporal gyrus, inferior frontal gyrus, caudate, and aMCC (Figure 4). In contrast, PCG connectivity with inferior parietal lobe and contralateral PCG was higher at post-intervention compared to baseline.

Next, we tested whether baseline pain severity and functional interference was associated with PCG connectivity at baseline and post-intervention (Table 3). Higher pain severity at baseline was associated with stronger PCG connectivity with cerebellum and medial frontal gyrus, and lower PCG connectivity with precentral gyrus and superior frontal gyrus at baseline. Pain interference was not associated with PCG connectivity at baseline. Higher baseline pain severity was associated with stronger PCG connectivity with middle temporal gyrus and inferior parietal lobe, and lower PCG connectivity with occipital lobe and medial inferior parietal lobe at post-intervention. Higher baseline functional interference was associated with stronger PCG connectivity with inferior parietal lobe and inferior temporal lobe, and lower PCG connectivity with a lateral region of inferior parietal lobe and precentral gyrus at post-intervention.

Finally, we tested whether baseline pain severity or interference was associated with changes in PCG connectivity between baseline and post-intervention (Table 3). Higher pain severity at baseline was associated with lower connectivity of PCG with the superior parietal lobe, cerebellum, and PCC from baseline to post-intervention (Figure 5, upper row), and with stronger PCG connectivity with middle frontal gyrus, contralateral PCG, hippocampus, and a separate cluster in the cerebellum. Higher pain interference at baseline was associated with decreased PCG connectivity with superior parietal lobe and increased PCG connectivity with inferior parietal lobe, superior temporal gyrus, posterior PCG, and brainstem from baseline to post-intervention (Figure 5, lower row).

Discussion

This pilot investigation demonstrates the feasibility, therapeutic promise, and brain basis of a 12-week meditative approach for OUD patients undergoing MMT. We found reductions in self-reported pain, opioid craving, anxiety, depression, and saliva cortisol in OUD patients after treatment sessions. Further, pain task-related activation in a key region of the pain neuromatrix—the PCG—decreased from pre- to post-intervention. At baseline, the PCG showed positive resting-state connectivity with other regions of the pain neuromatrix, but this pattern changed post-treatment. Baseline pain severity scores were associated with PCG connectivity both at pre- and post-treatment, and with the change from pre- to post-treatment. Our preliminary findings that this intervention can reduce self-reported pain and modulate the pain neuromatrix suggest a promising complementary approach to assist OUD patients burdened with pain.

On average, OUD patients in our sample reported substantial pain (4.8 of 10), consistent with previous findings that many OUD patients endorse chronic pain. Higher pain levels have been associated with worse outcomes among patients with substance use disorders, including relapse and reduced quality of life [8]. Here, we observed that a meditative intervention with relaxation exercises can reduce pain, anxiety, depression, and opioid craving among OUD patients on MMT. Notably, we found that initial decreases in craving rebounded midway through treatment, then decreased again; reasons for these changes remain unclear but could be related to temporary setbacks that are normal during the course of MMT. This pattern highlights the clinical importance of

Table 2. Resting-state functional connectivity results for left and right postcentral gyrus (PCG) at pre-intervention baseline, and from pre- to post-intervention

Contrast Seed	Direction	Target Region	Brodmann Area	x	y	z	Cluster Extent	Z-Score
All participants: Functional connectivity at baseline (i.e., pre-intervention)								
Left PCG	Positive							
		Left PCG	2	−58	−32	44	168	3.85
		Left inferior parietal lobe	40	−42	−36	44	43	3.76
		Right inferior parietal lobe	40	60	−26	26	22	3.51
		Left PCG	3	−44	−26	40	14	3.71
		Left PCG	40	−62	−24	20	14	3.56
		Left inferior parietal lobe	2	−52	−28	34	12	3.27
		Left inferior frontal gyrus	9	−50	6	14	12	3.91
		Right inferior parietal lobe	40	60	−34	40	10	3.51
		Left inferior parietal lobe	2	−52	−38	40	10	3.41
		Left cerebellum (anterior lobe)	N/A	−32	−44	−32	8	3.15
		Left PCG	40	−52	−32	52	8	3.47
		Left cerebellum (anterior lobe)	N/A	−18	−50	−32	8	3.43
		Left inferior frontal gyrus	44	−58	8	22	8	3.18
		Left middle frontal gyrus	9	−52	12	34	6	3.18
		Left precentral gyrus	9	−52	2	38	6	3.53
Right PCG	Positive							
		Right inferior parietal lobe	40	66	−34	22	169	3.92
		Right PCG	3	60	−26	44	12	3.50
		Left PCG	40	−62	−28	20	11	3.71
		Left inferior parietal lobe	1	−62	−26	−26	9	3.59
		Right brainstem	N/A	8	−32	−52	8	3.13
		Right middle temporal gyrus	22	48	−58	2	8	3.43
		Left inferior parietal lobe	40	−58	−28	34	6	3.27
		Left dorsal posterior insula	13	−42	−6	−2	5	3.44
Right PCG	Negative							
		Left middle frontal gyrus	9	−37	22	40	12	3.45
		Right frontal lobe	24	20	2	28	8	3.13
Left PCG	Negative							
		Right superior temporal gyrus	22	48	−18	2	8	3.22
		Right posterior cingulate cortex	29	8	−58	8	8	3.48
All participants: Change in functional connectivity from pre- to post-intervention								
Left PCG	Pre > Post							
		Right superior temporal gyrus	38	34	8	−38	8	3.46
		Right inferior frontal gyrus	47	54	22	2	8	3.31
Right PCG	Pre > Post							
		Left caudate	N/A	−18	−18	22	8	3.46
		Left anterior middle cingulate cortex	24	−6	8	28	8	3.15
Left PCG	Post > Pre							
		Left inferior parietal lobe	40	−52	−28	48	216	3.97
		Right PCG	2	60	−32	40	8	3.09
Right PCG	Post > Pre							
		Right PCG	1	66	−20	32	266	4.18
		Left PCG	40	−62	−14	20	5	3.23

All reported results are significant at the whole-brain corrected threshold (familywise error corrected using Monte Carlo simulations; voxel-wise threshold $P < .001$ and cluster-level correction (cluster minimum = 5 voxels). Cluster extent refers to the number of contiguous voxels in a cluster and the minimum cluster size was determined to be 5 voxels. Coordinates (x, y, z) refer to the anatomical location in 3D brain space, reported in MNI convention, at the peak maximally activated voxel within the cluster. Anatomical location of the peak location is reported using Brodmann areas. Note that separate target regions can have separate significant clusters within the same target region, particularly for anatomically large cortical regions. Test statistic given as a Z-score, which refers to the z statistic at the peak coordinate location. For baseline connectivity patterns, the Z-score was computed from the *t*- and *P* values derived from the group-level one-sample *t*-test. Higher Z-scores represent stronger connectivity between brain regions. For pre-post changes in connectivity, the Z-score was computed from the *t*- and *P* values derived from the group-level paired-samples *t*-test. Higher Z-scores represent greater pre-post intervention changes in functional connectivity between regions.

monitoring drug craving and mood measures throughout treatment; such data could be used as input to tailor this intervention. We also found pre-to post-session reductions in cortisol, a marker of HPA axis function [52]. Interestingly, prior treatment studies in chronic pain patients have revealed parallel reductions in self-reported pain severity and cortisol levels [53]. Previous studies have also linked elevated cortisol levels with a higher rate of relapse among individuals with substance use disorders [54]. A study of this meditative intervention in

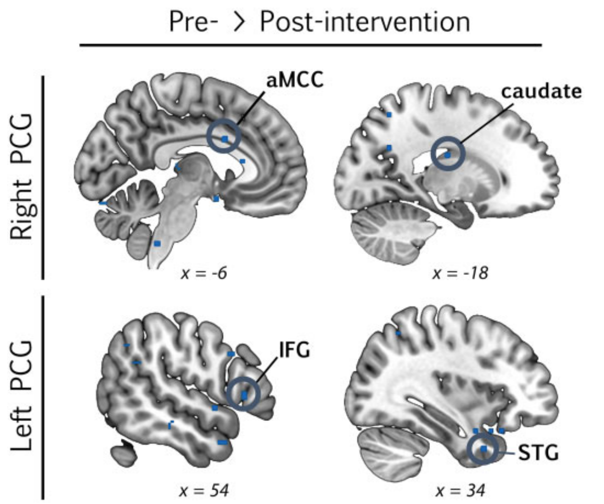

Figure 4. Reduced functional connectivity of the pain neuromatrix after the 12-week intervention (i.e., pre > post). Pain neuromatrix connectivity was estimated using seed-based resting-state functional connectivity of the left and right postcentral gyrus (PCG) with the rest of the brain. Image thresholded at $P <$ .01 uncorrected for display purposes. Regions indicated with a circle reach the whole-brain corrected threshold for reduced (blue) strength of connectivity (*pFWE* < 0.05). See Table 2 for full list of significant results. aMCC = anterior middle cingulate cortex; IFG = inferior frontal gyrus; STG = superior temporal gyrus.

children with cancer found that post- (vs. pre-) session pain scores on a 0–10 VAS scale decreased among 85% of those who received the intervention, and 96% reported decreased post-session pain scores when pre-session scores were >5; furthermore, median pain scores decreased by 40%, more so for older than younger children [36]. Our working hypothesis is that this intervention may reduce pain and cortisol levels through active engagement of *intrinsic* and *extrinsic* cognition/affective processing, compared with more passive and self-focused interactions [55]. Specifically, this therapist-assisted VR intervention led the OUD patient to modify his/her own internal psychobiological state *and* to believe that his/her success in this regard was also helping others (i.e., children with cancer).

It is important to distinguish this meditative intervention from other modalities such as mindfulness and yoga. Whereas mindfulness uses intentional and non-judgmental conscious awareness of the present moment and yoga incorporates physical postures, breathing control, and meditation/relaxation, Martial Arts Therapy (while incorporating elements of both interventions) adds core concepts of “Power, Peace, and Purpose”. ***Power*** comes from introducing an expanded element controlling one’s situation. The mind-body movements coalesce to move the individual from passive acceptance of one’s predicament to active engagement toward change. ***Peace*** derives from acceptance of one’s current situation and can mitigate negative feelings that often create behavioral stagnation. ***Purpose*** introduces elements of conviction and positive value for one’s existence and situation. It can help to transcend one’s situation and transform benign activity into something greater than the sum of its parts. Preliminary studies incorporating similar meditative interventions inspired by martial arts have shown promise in pain reduction [35, 36].

In addition to reductions in self-reported pain, there was a pre- to post-intervention reduction in pain task-related activation in the left PCG, a key region of the pain neuromatrix. Resting-state connectivity of the pain neuromatrix also changed from pre- to post-intervention, with reductions in connectivity between the PCG and other key regions (e.g., aMCC, caudate). The left PCG was the only pain neuromatrix ROI that significantly decreased in pain task-related activation from pre- to post-intervention. Left PCG activation was also positively correlated with baseline pain severity and cortisol levels. The PCG is a major part of the somatosensory cortex, implicated in perception of physical sensations from the body, including pain. The PCG is involved in anticipating and recognizing the location and intensity of pain [56], and may be involved in the development and/or maintenance of chronic pain [57].

Prior imaging studies have implicated the PCG in chronic pain and substance use disorders, including morphometric studies showing smaller PCG volume among polydrug users compared to non-users [58]. Smaller PCG volumes have also been reported in patients with chronic pain [59], and the PCG is consistently activated in fMRI studies of experimentally induced non-thermal pain [60]. Further, a study of individuals with cocaine use disorder found a decrease in PCG activity during a cognitive control task (i.e., Stroop) following a 12-week cognitive-behavioral therapy (CBT) and contingency management intervention [61]. In a follow-up study, greater pre- to post-CBT reductions in PCG activity were associated with longer duration of drug abstinence [8]. These findings suggest the PCG is relevant for both chronic pain and addiction, and may be treatment-responsive. A review of meditation interventions [10] suggested that meditation can attenuate pain ratings via reduced pain-related activation in the PCG, and experienced meditators show larger PCG gray matter volumes compared to less-experienced mediators. Results of the present study suggest a meditative intervention can reduce pain and modulate activity and connectivity of the PCG in OUD patients.

At baseline, the PCG showed positive connectivity with other regions of the pain neuromatrix, but this pattern changed post-treatment. In particular, PCG connectivity with the aMCC and caudate was lower post-intervention. The aMCC is associated with cognitive control of movement generation and emotional awareness, and encoding intensity of noxious pain [15]. The caudate is involved in planning movement execution and in sensing and suppressing pain [62, 63]. We also found higher

Table 3. Baseline pain severity and functional interference (Brief Pain Inventory) scores associated with resting-state functional connectivity of the postcentral gyrus (PCG) at pre- and post-intervention, and changes between pre- and post-intervention

Contrast Seed	Direction	Target Region	Brodmann Area	x	y	z	Cluster Extent	Z-score
Baseline pain severity associated with functional connectivity at baseline (i.e., pre-intervention)								
Left PCG	Higher pain severity, higher connectivity	Left cerebellum	N/A	−46	−64	−24	8	3.39
Right PCG	Higher pain severity, higher connectivity	Medial frontal gyrus	32	0	6	48	12	3.91
Left PCG	Higher pain severity, lower connectivity	Left precentral gyrus	4	−38	−24	−46	8	3.11
Right PCG	Higher pain severity, lower connectivity	Right superior frontal gyrus	6	20	8	54	8	3.14
Baseline pain functional interference associated with functional connectivity at baseline (i.e., pre-intervention)								
Left PCG	Higher pain interference, higher connectivity	No significant clusters						
Right PCG	Higher pain interference, higher connectivity	No significant clusters						
Left PCG	Higher pain interference, lower connectivity	No significant clusters						
Right PCG	Higher pain interference, lower connectivity	No significant clusters						
Baseline pain severity associated with functional connectivity at the post-intervention time point								
Left PCG	Higher pain severity, higher connectivity	Left inferior parietal lobe	1	−52	−26	44	10	3.44
Right PCG	Higher pain severity, higher connectivity	Right middle temporal gyrus	37	54	−64	0	12	3.66
Left PCG	Higher pain severity, lower connectivity	Left inferior parietal lobe	1	−46	−28	44	6	3.32
Right PCG	Higher pain severity, lower connectivity	Left occipital lobe	18	−32	−70	−6	8	3.10
Baseline pain functional interference associated with functional connectivity at the post-intervention time point								
Left PCG	Higher pain interference, higher connectivity	Left inferior parietal lobe	2	−52	−26	46	34	4.30
Right PCG	Higher pain interference, higher connectivity	Right inferior temporal lobe	20	44	−44	−18	20	4.00
Left PCG	Higher pain interference, lower connectivity	Left inferior parietal lobe	40	−64	−32	34	8	3.09
Right PCG	Higher pain interference, lower connectivity	Right precentral gyrus	6	40	−14	64	6	3.12
Baseline pain severity associated with changes in functional connectivity from pre- to post-intervention								
Left PCG	Higher pain severity, greater pre- to post reductions in connectivity	Right cerebellum (posterior lobe) N/A 14 –58 -24 8 3.44						
		Left superior parietal lobe 7 –22 -52 48 6 3.45						
Right PCG	Higher pain severity, greater pre- to post reductions in connectivity	Right posterior 23 8 –38 8 8 4.42 Cingulate cortex						
		Cerebellum (posterior lobe) N/A 0 –70 -18 8 3.38						
Left PCG	Higher pain severity, greater pre- to post increases in connectivity	Right precentral gyrus 6 40 –14 60 8 3.31						
		Right middle frontal gyrus 11 20 40 –14 6 3.36						
Right PCG	Higher pain severity, greater pre- to post increases in connectivity	Left hippocampus N/A -26 –18 -12 8 4.26						
		Left cerebellum N/A -18 –78 -52 8 3.09						
Baseline pain functional interference associated with changes in functional connectivity from pre- to post-intervention								
Left PCG	Higher pain interference, greater pre- to post reductions in connectivity	Left superior parietal lobe 7 –18 -60 48 8 3.39						
		Left superior parietal lobe 7 –12 -64 64 8 3.37						
		Left superior parietal lobe 7 –24 -64 60 8 3.72						

(continued)

Table 3.. continued

Contrast Seed	Direction	Target Region	Brodmann Area	x	y	z	Cluster Extent	Z-score
Right PCG	Higher pain interference, greater pre- to post reductions in connectivity	No significant clusters						
Left PCG	Higher pain interference, greater pre- to post increases in connectivity	Right precentral gyrus 4 40 –18 60 10 4.41						
		Right superior temporal gyrus 42 60 –32 14 8 3.47						
Right PCG	Higher pain interference, greater pre- to post increases in connectivity	Left inferior parietal lobule. 40 –64 -24 34 12 3.27						
		Left Brainstem N/A -14 –34 -58 11 3.32						

All reported results are significant at the whole-brain corrected threshold (familywise error corrected using Monte Carlo simulations; voxel-wise threshold $P < .001$ and cluster-level correction (cluster minimum = 5 voxels). Cluster extent refers to the number of contiguous voxels in a cluster and the minimum cluster size was determined to be 5 voxels. Coordinates (x, y, z) refer to the anatomical location in 3 D brain space, reported in MNI convention, at the peak maximally activated voxel within the cluster. Anatomical location of the peak location is reported using Brodmann areas. Note that separate target regions can have separate significant clusters within the same target region, particularly for anatomically large cortical regions. Test statistic given as a Z-score, which refers to the z statistic at the peak coordinate location. The Z-score was computed from the *t*- and *P* values derived from group-level regression analyses (BPI scores associated with functional connectivity or changes in functional connectivity). Higher Z-scores represent stronger connectivity between brain regions in those with higher BPI scores, or greater pre-post increases in connectivity in those with higher BPI scores. BPI = Brief Pain Inventory.

baseline cortisol levels were associated with greater post-treatment pain task-related insular activation. A primary role of the insula is pain perception including arousal and attention to nociceptive stimuli [20].

In addition to overall changes in PCG activation and connectivity, we found that baseline pain severity and interference scores were associated with changes in PCG connectivity from pre- to post-intervention. Patients with both higher pain severity and pain functional interference showed greater reductions in PCG–superior parietal lobe connectivity. The superior parietal lobe is involved in the perception and modulation of painful somatosensory sensations [64]. Furthermore, higher baseline pain severity was associated with less PCG–PCC connectivity. Previous studies have reported the PCC's possible role in modulating the conscious experience of pain [65]. Specifically, higher PCC activity has been associated with lower pain ratings [15]. Therefore, reduced PCG-PCC connectivity may indicate greater regulatory control of the PCC over sensory pain-related processing in the PCG either over time or due to the meditative intervention.

Our investigation should be interpreted in the context of limitations. This study was preliminary using a one-arm, unblinded design with a small sample. Thus, randomized controlled trials in larger samples are needed to evaluate efficacy of this intervention and to explore its mechanisms of effect. Also, the sample was predominantly female, which may relate to differences in pain perception and pain neuromatrix activity. Sex effects should be explored in future studies. Next, although all OUD patients were on MMT, it is unclear whether similar effects would be found for patients receiving other forms of OUD treatment. Furthermore, clinical

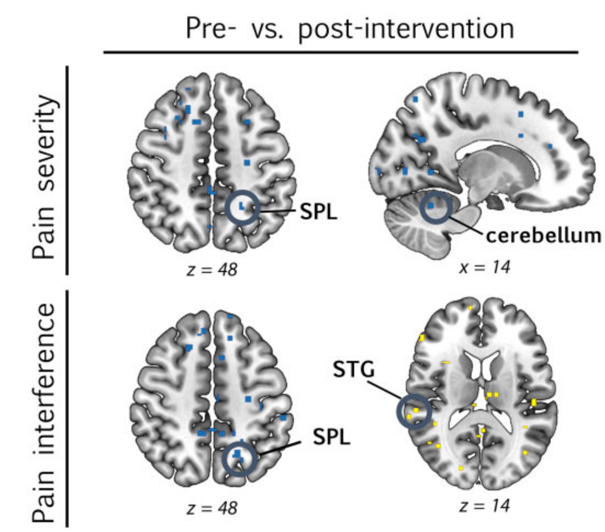

Figure 5. Pain severity and pain functional interference at baseline is associated with changes in connectivity of the pain neuromatrix from baseline to post-intervention. Higher pain severity (upper row) and pain functional interference (lower row) at baseline is associated with greater reductions (blue) or increases (yellow) in pain neuromatrix connectivity from pre- to post-intervention. Pain neuromatrix connectivity was estimated using seed-based resting-state functional connectivity of the left and right postcentral gyrus (PCG) with the rest of the brain. Image thresholded at $P < .01$ uncorrected for display purposes. Regions indicated with a circle reach the whole-brain corrected threshold for reduced (blue) or increased (yellow) strength of connectivity (*pFWE*<0.05). See Table 3 for full list of significant results. SPL =superior parietal lobe; STG = superior temporal gyrus.

heterogeneity of the sample may have restricted our ability to observed changes over time in cortisol or CRP levels, and/or reported pain, anxiety, depression, and/or opioid craving.

The results of this feasibility study suggest a VR-based, meditative intervention is a promising approach for reducing pain ratings and modulating pain neuromatrix activity and connectivity among OUD patients. This intervention may be a beneficial part of a multidisciplinary pain and addiction management program.

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Authors' Contributions

M.M.F. and N.M.L. drafted key sections of the manuscript. A.M. is a martial artist who conducted some intervention sessions, and was involved in imaging data collection and analysis. E.G. and M.B. contributed to the study concept, development of the VR software, and supervised activities of the martial artists. H.A.M. conceptualized and supervised the brain imaging and data analyses, and edited the manuscript. M.K.G. conceptualized and designed the study, supervised all nonimaging data collection, management and analysis, and edited the manuscript.

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Martial Arts-Based Therapy Curriculum Reduces Stress, Emotional, and Behavioral Problems in Elementary Schoolchildren During the COVID-19 Pandemic: A Pilot Study

Hilary A. Marusak[1,2], Breanna Borg[1], Austin Morales[1], Jamila Carrington Smith[3], Kelly Blankenship[3], Junior Lloyd Allen[4], Elimelech Goldberg[3,5], and Martin H. Bluth[3,6,7]

ABSTRACT— This exploratory study examined the impact of Heroes Circle, a martial arts-based curriculum on stress, emotional, and behavioral problems in elementary school children. While students completed classroom surveys at baseline, post-curriculum surveys were collected from teachers, students, and parents/guardians 2 and 5 months after COVID-19-related school shutdowns. Satisfaction with the curriculum was high among those who received the intervention. Children reported increased mindfulness and decreased stress over the school year. Most children (77%) were still using the program's techniques and reporting benefits 5 months later, including lower internalizing symptoms and COVID-19-related fears. These patterns were not observed at the control school.

[1]Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University
[2]Merrill Palmer Skillman Institute for Child and Family Development, Wayne State University
[3]Kids Kicking Cancer
[4]School of Social Work, Wayne State University
[5]Department of Pediatrics, School of Medicine, Wayne State University
[6]Department of Pathology, School of Medicine, Wayne State University,
[7]Department of Pathology, Maimonides Medical Center

Address correspondence to Hilary A. Marusak, Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, MI; e-mail: hmarusak@med.wayne.edu

Mindfulness-based school programs are a promising approach for reducing stress and improving well-being among K-12 students (Semple, Droutman, & Reid, 2017). Such programs cultivate self-awareness and self-regulation by focusing attention on thoughts, emotions, breath, and other internal sensations (Hölzel et al., 2011). These programs have helped to reduce stress and anxiety, while also improving self-control, attention, and academic achievement (Caballero et al., 2019). Studies also underscored significant outcomes in treating common childhood emotional and behavioral disorders, such as anxiety and attention deficit hyperactivity disorder (van der Oord, Bögels, & Peijnenburg, 2012). One key explanation is that these childhood changes were mediated by functional changes in brain regions that affect attentional control, emotion regulation, body awareness, and self-reference (Bauer et al., 2019; Marusak et al., 2018).

One particular program, martial arts, is a fun program that engages children due to its pairing of mindfulness training with physical movement (Yang & Conroy, 2018). Traditional martial arts address physical and mental developments while emphasizing respect, self-discipline, focus, and character development. The themes present in martial arts may resonate well with children from disadvantaged backgrounds, who may feel they have limited control over their lives. Engaging with children from lower-income communities or who have higher initial emotional or behavioral problems is critical because research shows that these

Fig. 1. Children in the Heroes Circle (HC) program practicing the Breath Brake. The Breath Brake is a breathing exercise that allows children to take control over their stress and anxiety. This image was approved by the school principal and superintendent.

groups are at the highest risk of falling behind academically. Finally, studies showed that martial arts training also reduced pain and emotional distress among children with cancer, other chronic diseases, and their siblings (ages 5–17; Bluth, Thomas, Cohen, Bluth, & Goldberg, 2016; Marusak et al., 2020).

Given that the coronavirus disease 2019 (COVID-19) pandemic has resulted in school closures, a transition to remote teaching and learning, and various other forms of compounded stress, and uncertainty, on K-12 students and educators (Mustafa, 2020), this exploratory study investigated whether a novel martial arts-based meditative school program—the Heroes Circle (HC, Figure 1; see Appendix S1)—reduced stress, emotional, and behavioral problems among elementary schoolchildren. Parallel measures were collected in a control school, wherein students did not participate in the HC program. The COVID-19 pandemic has worsened emotional and behavioral problems (Gassman-Pines, Ananat, & Fitz-Henley, 2020) and exacerbated already-existing disparities in educational outcomes among lower-income and minority youth (Masonbrink & Hurley, 2020); challenges that are particularly salient among younger students who may have limited attention and self-regulation capacity. As such, school-wide interventional programs are needed to mitigate the worsened emotional and behavioral problems and widening achievement gap, particularly among younger children from disadvantaged backgrounds (Hashim, Kane, Kelley-Kemple, Laski, & Staiger, 2020). The following hypotheses guided this study: (1) satisfaction with the HC program would be higher than at the control school; (2) children who participate in the HC (but not in the control group) would demonstrate increased mindfulness and decreased stress and emotional and behavioral problems over the school year; and (3) report lower COVID-19-related fear.

MATERIAL AND METHODS

Overview

This exploratory study focused on three Detroit-area (Michigan, USA) elementary schools (two public, one private) for the 2019–2020 academic year (Figure 2a, timeline). Students at Schools 1 (public) and 3 (private) participated in the HC. School 2, which was in the same district as School 1, was selected as the control school (Appendix S2) and did not receive the HC. The local institutional review board approved all study procedures (see Appendix S3 for more details).

HC Program

The HC was adapted for the school environment from standard Kids Kicking Cancer (KKC) classes (Bluth et al., 2016; Marusak et al., 2020). KKC uses a martial arts-based approach to help children with cancer and other chronic illnesses cope with pain and anxiety. In this program, the students were taught visualization and relaxation techniques and the "Breath Brake," a breathing exercise that allows children to control their pain and anxiety. The mantra of KKC/HC is "Power. Peace. Purpose," which emphasizes respect, self-regulation, discipline, and a feeling of empowerment.

Surveys

Two hundred and ninety-two students and 17 teachers across all three schools completed surveys in the classroom at baseline (T0; October 2019; Table 1). During May 2020—2 months following COVID-19—related school shutdowns, 18 teachers and 64 child–parent dyads completed T1 surveys. Another installment of survey data collection was done in August 2020 (T2) for parents and children to test for continued use of HC techniques and whether these techniques conferred benefit for anxiety or COVID-related outcomes (Table 2). Teachers reported on demographics, teaching experience, and program satisfaction at T1. At T1 and T2, children reported on program satisfaction, continued use of the HC techniques, and COVID-related fears, behaviors, and impact. At T0, T1, and T2, children reported on outcome variables (i.e., stress, internalizing, externalizing, and attention problems) and the purported process variable (mindfulness). At T1, students and teachers were asked to provide qualitative feedback on the aspects they liked and disliked about the program. Figure 2 highlights the survey time points and measures.

Data Analyses

Descriptive phenomenology was used to assess the qualitative responses. Overall analyses examined program

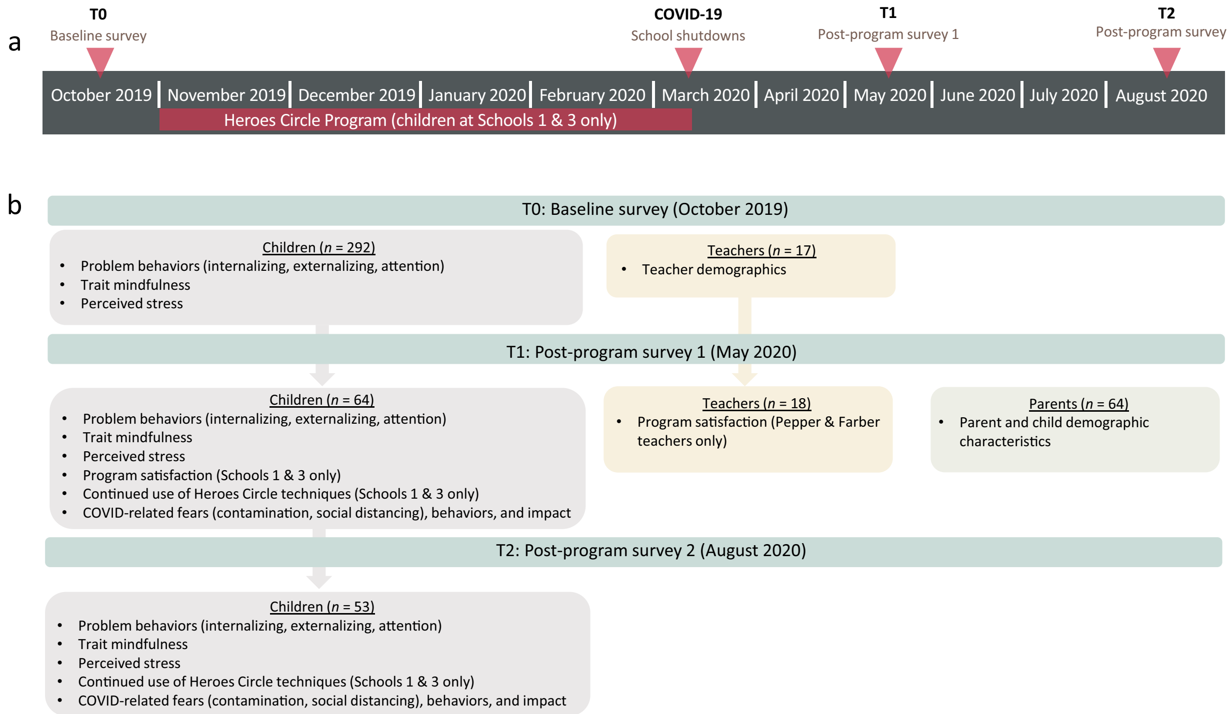

Fig. 2. Survey study timeline. (a) By month. (b) Survey data collection time points and measures of interest. The Heroes Circle (HC) program was administered at Schools 1 and 3 only. School 1 is a public school, and School 3 is a nearby private school (within 5 miles). School 2, a public school in the same district as School 1, served as the control school.

satisfaction and continued use of HC techniques over time (T1 vs. T2) using descriptive statistics and chi-square tests. Paired samples t-tests were conducted on mindfulness and outcome variables to examine within-group change over time from pre- to post-intervention. Correlations between change scores in mindfulness and changes in other outcomes of interest were examined following prior work (Flook, Goldberg, Pinger, Bonus, & Davidson, 2013). We also explored correlations among continued use of HC techniques, mindfulness, and outcome variables. This is an exploratory study and was likely underpowered.

RESULTS

Satisfaction With the HC Curriculum

Satisfaction with the HC curriculum was high among students (Figure 3a) and teachers (Figure 3b), and student satisfaction with the HC was higher than what was reported in the control group. Qualitative analyses showed that students reported becoming more aware of their behaviors, they liked the Breath Brakes, and the activities they completed were insightful. However, some students recalled that some of the activities were not as engaging. A large majority of teachers who observed the HC in their classroom highlighted the timeliness and relatability of the activities in conjunction with the students' lives.

Continued Use of HC Techniques

At T1, the majority of students who participated in the HC still reported using Breath Brakes and feeling the benefit from HC techniques (see Figure 4). Though there was a nonsignificant change at T2, most children reported still using Breath Brakes and feeling the benefit from the techniques—5 months after formal instruction ended (see Figure 4).

Outcome Variables

Overall, students who participated in the HC reported a significant decrease in perceived stress over the school year. There was no significant change in internalizing, externalizing, or attention problems over the school year among the students who participated in the HC nor at the control school, and no changes between T1 and T2 in either group.

Process Variable

Students who participated in the HC reported a significant increase in mindfulness over the school year. Among students who participated in the HC, those with higher externalizing problems at baseline reported greater increases in mindfulness over the school year. Perceived stress, internalizing, and attention problems at baseline were not associated with a change in mindfulness over

Table 1
Child and Teacher Characteristics at Baseline (T0; October 2019)

Children (n = *292*)	*Public schools* School 1 (N = 131)	*Public schools* School 2 (control) (N = 109)	*Difference statistic: School 1 versus School 2*	*Private school* School 3 (N = 52)	*Difference statistic: Schools 1 and 2 versus 3*
Age, *M* years (*SD*)	7.65 (0.77)	7.83 (0.78)	$t(238) = 1.8$, $p = .067$	7.9 (.8)	$t(290) = 1.4$, $p = .16$
Gender, *n* (%)			**$\chi^2(1) = 4.13$, $p = .042$**		$\chi^2(1) = .02$, $p = .89$
Female	49 (37%)	55 (50%)		22 (42%)	
Male	82 (63%)	54 (50%)		30 (58%)	
Grade, *n* (%)			**$\chi^2(1) = 19.7$, $p < .001$**		**$\chi^2(2) = 50.2$, $p < .001$**
Second grade	61 (47%)	21 (19%)		20 (39%)	
Third grade	70 (53%)	88 (81%)		22 (42%)	
Fourth grade	0	0		10 (19%)	
Race/ethnicity, *n* (%)			$\chi^2(1) = 3.15$, $p = .68$		**$\chi^2(5) = 149.6$, $p < .001$**
Black non-Hispanic	94 (72%)	75 (69%)		1 (2%)	
White non-Hispanic	9 (7%)	5 (5%)		38 (73%)	
Hispanic	5 (4%)	5 (5%)		1 (2%)	
Asian	8 (6%)	6 (5%)		0	
Other/prefer to not answer	15 (11%)	18 (16%)		12 (23%)	

Teachers (n = *17*)	*Public schools* School 1 (N = 6)	*Public schools* School 2 (control) (N = 6)	*Difference statistic: School 1 versus School 2*	*Private school* School 3 (N = 5)	*Difference statistic: Schools 1 and 2 versus 3*
Gender, *n* (%)			N/A		**$\chi^2(1) = 5.4$, $p = .02$**
Female	6 (100%)	6 (100%)		3 (60%)	
Male	0	0		2 (40%)	
Grade, *n* (%)			$\chi^2(1) = 3.4$, $p = .56$		$\chi^2(2) = 2.6$, $p = .27$
Second grade	3 (50%)	2 (33%)		2 (40%)	
Third grade	3 (50%)	4 (67%)		2 (40%)	
Fourth grade				1 (20%)	
Race/ethnicity, *n* (%)			$\chi^2(1) = 1.1$, $p = .3$		$\chi^2(1) = .44$, $p = .51$
Black non-Hispanic	0	1 (17%)		0	
White non-Hispanic	6 (100%)	5 (83%)		5 (100%)	
Number of children, *M* (*SD*)	25.8 (1.6)	23.5 (.55)	**$t(10) = 3.37$, $p = .007$**	17 (7.2)	$t(4.18) = 2.29$, $p = .08$
Overall teaching experience, *n* (%)			$\chi^2(3) = 6.29$, $p = .099$		$\chi^2(4) = 5.96$, $p = .2$
Less than 1 year	1	0		0	
1–2 years	0	1		1	
3–5 years	0	0		1	
6–10 years	0	3		1	
Over 10 years	5	2		1	

the school year. Those who participated in the HC showed greater increases in mindfulness over the academic year, and demonstrated greater *decreases* in perceived stress, internalizing, externalizing, and attention problems over the school year (Figure 5a). Remarkably, students who showed a greater increase in mindfulness over the school year also reported that COVID-19 had a lower impact on their lives at T1 and reported lower COVID-19 fears of contamination at T2 (Figure 5b).

Exploratory Correlation Analyses

At T2, students who reported more frequently using the Breath Brake also reported *lower* internalizing symptoms. At T2, students who reported feeling like a powerful martial artist reported less fear of COVID-19 contamination and less fear of social distancing.

DISCUSSION

This exploratory study provides preliminary evidence that the HC, a novel school-based martial arts program, reduces stress and emotional and behavioral problems among elementary schoolchildren. There was an overall high level of satisfaction with the HC among children and teachers, with 100% of children and 83% of teachers recommending this program to another child or teacher. More important, 85%

Table 2
Child Characteristics at the Post-Program Survey Time Point (T1; May 2020)

Children (n = 64)	*Public schools* School 1 (N = 30)	*Public schools* School 2 (Control) (N = 16)	*Difference statistic: School 1 versus School 2*	*Private school* School 3 (N = 18)	*Difference statistic: Schools 1 and 2 versus 3*
Age, *M* years (*SD*)	8 (.61)	8.4 (.62)	$t(44) = 1.8, p = .08$	8.4 (.78)	$t(62) = 1.5, p = .12$
Gender, *n* (%)			$\chi^2(1) = 3.38, p = .067$		$\chi^2(1) = 1.7, p = .2$
Female	7 (23%)	8 (50%)		9 (50%)	
Male	23 (77%)	8 (50%)		9 (50%)	
Grade, *n* (%)			$\chi^2(1) = 2.1, p = .15$		**$\chi^2(2) = 9.9, p = .007$**
Second grade	16 (53%)	5 (31%)		10 (55%)	
Third grade	14 (47%)	11 (69%)		5 (28%)	
Fourth grade	0	0		3 (17%)	
Race/ethnicity, *n* (%)			N/A		**$\chi^2(2) = 64, p < .001$**
Black non-Hispanic	30 (100%)	16 (100%)		0	
White non-Hispanic	0	0		16 (89%)	
Other/prefer to not answer	0	0		2 (11%)	
Parent's highest education level, *n* (%)			$\chi^2(4) = 2.1, p = .228$		**$\chi^2(5) = 21.9, p = .001$**
High school or equivalent	2	2		0	
Some college	9	9		4 (22%)	
2-year college degree	10	4		0	
4-year college degree	5	0		6 (33%)	
Master's degree	4	1		5 (28%)	
Doctorate	0	0		3 (17%)	

Note: Bolded values indicate significant differences ($p < 0.05$).

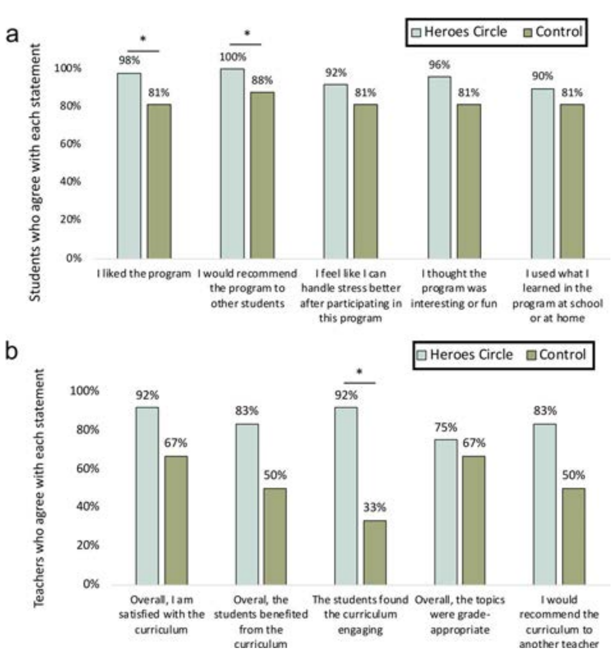

Fig. 3. Child (a) and teacher (b) satisfaction with the Heroes Circle (HC) program and in the control group as reported in May 2020 (T1). $^*p < .05$, chi-square test.

and 77% of children reported that they still used the HC techniques, such as the Breath Brake, 2 and 5 months after COVID-19-related school shutdowns. Children who continued to use HC techniques reported benefits such as lower internalizing symptoms and COVID-19-related fears up to 5 months later and had increased mindfulness and decreased perceived stress over the school year. These findings were supported by the qualitative data, which showed that the HC activities helped students become conscious of their emotions. Not surprisingly, the utilization of child-friendly and fun activities created a conducive environment that helped them retain these practices over time. Overall, although underpowered, study findings support the beneficial effects of a school-based martial arts program on social–emotional well-being among both socioeconomically disadvantaged and advantaged elementary schoolchildren.

Martial Arts Training Associated With Reduced Perceived Stress and Increased Mindfulness

The HC revealed decreased perceived stress over time whereas the control group showed no significant change. This finding is supported the extant literature about the impact of school-based martial arts programs on socioemotional well-being, resilience, self-efficacy, and self-regulation (Lakes & Hoyt, 2004). Students who participated in the HC reported increased mindfulness over time. It is suggestable that mindfulness training may be a "process" variable that is mediated by the positive effects of martial arts, and those

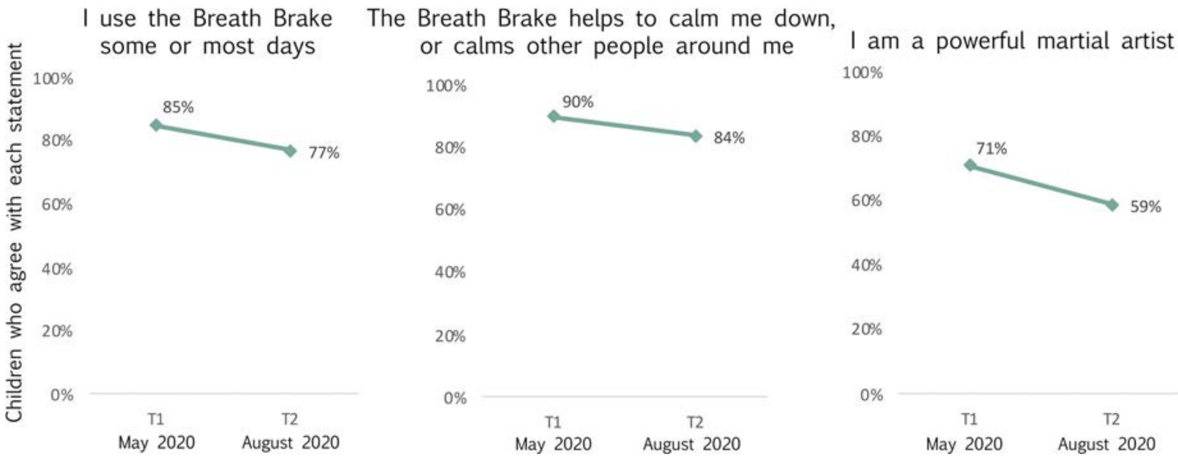

Fig. 4. Continued use of Heroes Circle (HC) program techniques in May and August 2020. Children were surveyed about their continued use of HC techniques and whether they perceived benefit in May and August 2020—2 and 5 months after COVID-19-related school shutdowns and the end of formal HC instruction, respectively. The drop in use of HC techniques over time was not statistically significant.

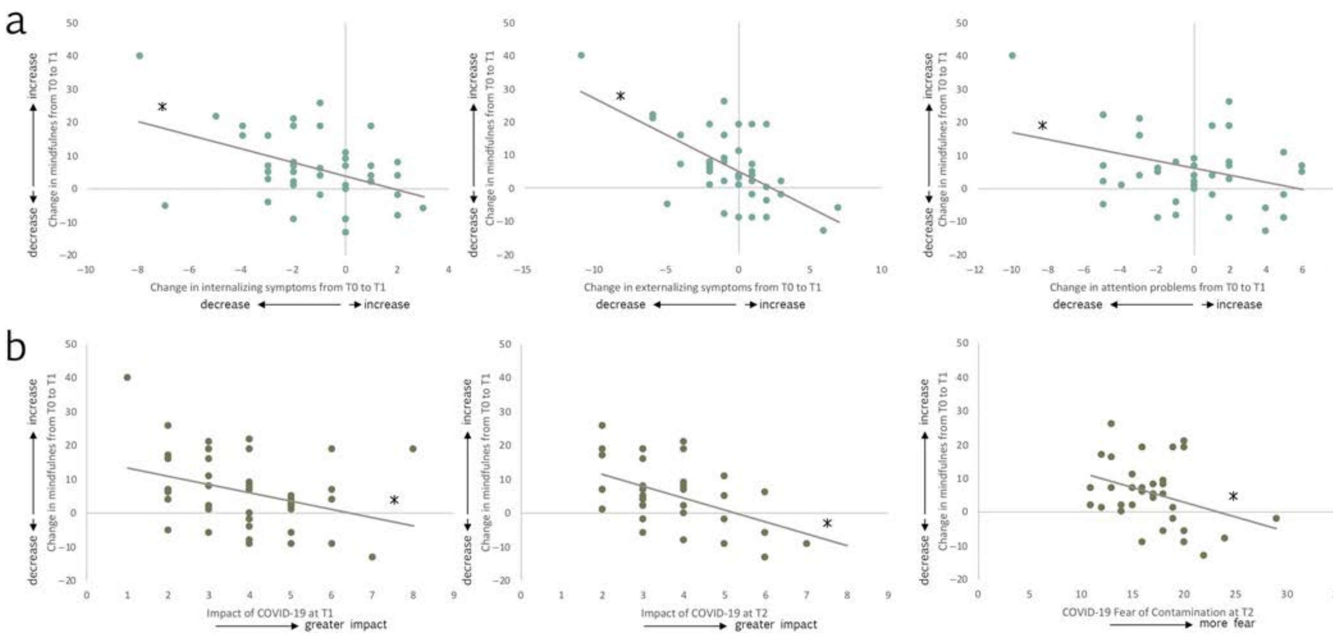

Fig. 5. Children in the Heroes Circle (HC) program who reported greater mindfulness increases over the school year reported greater decreases in problem behaviors (top row) and lower COVID-related fears and impact (bottom row). T0 surveys were completed before the HC program in October 2019; post-program surveys were completed in May (T1) and August 2020 (T2). COVID-10-related fears and impact measured using the Fear of Illness and Virus Evaluation (FIVE; Ehrenreich-May, 2020). Internalizing, externalizing, and problem behaviors measured using the Pediatric Symptom Checklist (PSC); trait mindfulness was measured using the Child and Adolescent Mindfulness Measure (CAMM). Change scores were computed by subtracting scores at T1 from T0.

who showed greater mindfulness improvements may be those who were more responsive to the program. Students with more externalizing problems at baseline showed the greatest increases in mindfulness, consistent with prior evidence that students with initially poorer executive functions benefit most from martial arts or mindfulness-based programs (Diamond & Lee, 2011). Intervening at the elementary school level helps mitigate widening achievement gaps. Likewise, greater mindfulness resulted in greater reductions in stress, internalizing, externalizing, and attention problems, further supporting the benefits of mindfulness for emotional and behavioral functioning. These findings' implications are substantial, considering that student learning is optimal in a non-disruptive classroom and that teacher stress and job satisfaction are tied to classroom functioning (Montgomery & Rupp, 2005).

Martial Arts for Coping With COVID-19-Related Stress

This study occurred during COVID-19 school shutdowns and provided a unique opportunity to investigate whether HC could help students cope with a novel, unpredictable, and uncertain stressor. Prior natural disasters (e.g., hurricanes) studies suggest that children were particularly vulnerable to stressors because their capacity to adapt independently was limited though their sensitivity to uncertainties was greater (La Greca et al., 2013). Children from disadvantaged backgrounds may be even more susceptible to enduring stress in the wake of large-scale stressors, including feelings of anxiety, helplessness, and insecurity (Weems et al., 2010). Our data suggest that the continued use of HC techniques may facilitate adaptive changes in children during the COVID-19 pandemic, such as lower fear and lower perceived impact. These adaptive changes may be attributed, in part, to an increased sense of control and agency associated with martial arts training. For example, using Breath Brakes helps children control their fears and anxieties to improve their self-perception like powerful martial artists who can conquer new challenges. It was also notable that students who showed greater mindfulness increases throughout the program reported lower COVID-19-related fear and perceived impact.

CONCLUSIONS

We report preliminary evidence that a grade-wide, school-based martial arts-based meditative/mindfulness program may reduce stress, emotions, and behavioral problems and mitigate the impact of COVID-19 on elementary schoolchildren. These benefits were accompanied by increases in children's mindfulness, which has been linked to better academic and mental health outcomes among youth (Caballero et al., 2019). Given that nearly all emotional and behavioral disorders begin during childhood (Kessler et al., 2005), martial arts-based programs may be a prophylactic approach for reducing the likelihood of developing psychopathology. Furthermore, the program appears to provide sustainability in that the initial intervention provided effects that lasted at least 5 months after the initial intervention. This has additional economic applications in school systems that are strained for resources. Although this study was not a randomized study design, the next step, given these interesting findings from these exploratory findings, is to design and implement a randomized, sufficiently powered protocol. School-based martial arts programs may help to level the playing field and diminish the achievement gap while improving child well-being and the broader learning environment.

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Conflict of interest

EG is the founder and global director of Kids Kicking Cancer (KKC), a nonprofit organization that developed this martial arts intervention. MHB is the global medical director of KKC. JCS and KB developed the Heroes Circle school-based curriculum. HAM has received previous grant funding from KKC, and this research was funded by a subcontract from KKC (EG) to HAM. The authors declare no other conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. The Heroes Circle Program.

Appendix S2. Control School.

Appendix S3. Student (A) and teacher (B) satisfaction with the HC program by school. School 1, public school. School 2, private school.

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Transformative Value: The Role of Volunteers in Creating Well-being in the Healthcare Service

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Laura Di Pietro[a], Veronica Ungaro [a], Maria Francesca Renzi[a], Bo Edvardsson[b]

[a]University of Roma Tre, Italy, laura.dipietro@uniroma3.it
[a]University of Roma Tre, Italy, veronica.ungaro@uniroma3.it
[a]University of Roma Tre, Italy, mariafrancesca.renzi@uniroma3.it
[B] Karlstad University, Sweden, bo.edvardsson@kau.se

ABSTRACT

The article aims to analyze the value creation process by zooming in on the volunteers' activities in a healthcare ecosystem. A qualitative approach is adopted, and an empirical investigation is carried out in collaboration with Kids Kicking Cancer Italia, an association operating in the pediatric oncology wards. Empirical data was collected through 17 in-depth interviews and the analysis of volunteers' diaries.
The study identifies the actors involved in the value creation process of volunteering activities within the healthcare ecosystem. Moreover, four categories of volunteers' value co-creation practices are identified, together with the well-being outcomes generated for each category of actors.

INTRODUCTION

So far, poverty, discrimination, inequality, and vulnerability contribute to feeding the modern society crisis. Innovative solutions are needed to respond to these turbulent times and foster a more inclusive society. In accordance with the transformative service research (TSR), an inclusive society is characterized by a high level of individual and collective well-being (Anderson *et al.*, 2014; Rosenbaum *et al.* 2012; Ostrom *et al.*, 2010). Hence, it becomes a research priority to identify value creation processes that pursue the re-humanization of services (Field *et al.*, 2021). In this regard, healthcare is one of the most important services linked to individuals' well-being (Ungaro *et al.*, 2021). It is also a relevant sector to study relationships, dynamics and potentialities of TSR (Ostrom *et al.* 2015).

In the healthcare ecosystem, volunteering and co-therapy activities support traditional medicine and are carried out through the collaboration of multiple actors (i.e. hospitals, patients, voluntary associations) who integrate their resources to reduce the negative feelings associated with the disease and enhance patient and families' well-being (Guglielmetti and Menicucci, 2020). The volunteer represents an important actor who can play a pivotal role in building a more responsive and resilient healthcare service ecosystem and contributing to providing services for vulnerable consumers (Field *et al.*, 2021). A volunteer is a person that voluntarily decides to carry out activities in favour of the general good and social well-being without an economic reward (European Youth Forum, 2012). According to the service research priorities identified by Field *et al.* (2021), the volunteer actor can contribute to elevating the healthcare ecosystem and transforming it into a sustainable service ecosystem. Indeed, volunteers are key actors in the value creation process of the healthcare ecosystem, but so far, their contribution has received limited attention in service research (Mulder *et al.*, 2015). Hence, it becomes a priority to analyze how and why volunteering and co-therapy activities can contribute to designing a sustainable healthcare service ecosystem, building social cohesion and societal resilience (Field *et al.*, 2021). In line with the call of Rosenbaum *et al.* (2011), the present study contributes to investigating the supportive role that volunteers operating for the non-government organization contributes to investigating the supportive role that volunteers operating for the non-government organization can provide in the specific field of healthcare. Although volunteers play essential roles in care services, their contributions have not been much focused on in service research.

This article aims to empirically analyze the value creation process by zooming in on the volunteers' activities in a healthcare ecosystem. More specifically, the empirical context is the provision of co-therapy services to hospitalized patients and the role of volunteers in creating sustainable healthcare services. The focus is on (a) identifying the categories of actors interacting with the volunteers in the value creation process and (b) describing how the volunteers co-create value by exchanging resources with the other actors, and (c) analyzing the related well-being outcomes. In this direction, the paper investigates the volunteers' role in co-creating transformative value and generating well-being outcomes for the whole ecosystem, as well as the broader perceptions of the charitable services provided as co-therapy within the hospitals.

The article provides two theoretical contributions. First, the study represents one of the first empirical research aimed to create new theoretical knowledge on sustainable service healthcare ecosystems focusing on the role of volunteers. Second, we contribute to TSR by identifying the main categories of well-being outcomes deriving from the co-creation process of volunteering activities carried out in the healthcare ecosystem.

Against the above backdrop, a qualitative approach is adopted, and an empirical investigation is carried out in collaboration with Kids Kicking Cancer (KKC) Italia, a volunteer's association operating in the paediatric oncology ward of many Italian hospitals. Empirical data was collected through in-depth interviews with volunteers and the analysis of one-year volunteers' diaries.

The article is organised as follow: first, an explanation of the methodology is provided to elucidate data collection and analysis; then, preliminary findings and discussion regarding the role of volunteers and the impact of their co-creation activities are presented; finally, authors outlined conclusions with limitation and future research.

THEORETICAL FRAMING

The study of service ecosystems' impact on human and planet well-being is an emerging priority for service research. The design of sustainable service ecosystems represents a pillar that needs to be deepened through empirical investigation, by analyzing three priorities: *large-scale and complex service ecosystem for transformative impact*; *platform ecosystems and marketplaces*; and *service for disadvantaged consumers and communities* Field *et al.*, (2021). To do research in line with these priorities, it is necessary to embrace a wider vision aimed to adopt a multi-stakeholder perspective to understand the contribution that each actor can play in developing a more sustainable value creation process in complex service ecosystem. According to this perspective, volunteers and volunteering associations are directly involved in transformative service (Mulder *et al.* 2015), especially the ones operating in the healthcare sector, contributing to create transformative and sustainable value for society. Healthcare service ecosystems evolve continuously and are characterized by high levels of complexity and specific actors (Frow et al 2019, Chandler and Vargo, 2011). A wide range of actors are involved in the process of co-creating value by combining and recombining resources, and developing coordinated collaboration mechanism at operational, political, social, economic, legal or ethical levels (Ciasullo et al, 2016: Polese and Capunzo, 2013). An important group that often are neglected is volunteers. They play an important role in healthcare in collaborating with and adding resources to the service provision, of particular importance for the well-being of engaged actors.

The European Volunteering Chart (European Youth Forum, 2012), answering to the need of a common and shared vision on the topic, defined the volunteers as "a person who carries out activities benefiting society, by free will. These activities are undertaken for a non-profit cause, benefiting the personal development of the volunteer, who commits their time and energy for the general good without financial reward". In Italy, the volunteers' role is regulated by the D.Lgs.117/2017 and he is defined as "A person which, by its own free choice, carries out activities in favour of the community and the common good, also for through an agency of the Third Party sector, making available his/her own time and ability to respond to the needs of people and communities benefiting from its action, in a personal way, spontaneous and free, without profit-making, not even indirect, and exclusively for the purposes of solidarity". Moreover, the activity of the person cannot be paid in any way even from the beneficiary, the institution of the Third-Party sector can reimburse only the expenditure documented based on the precondition established from the institution.

Hence, the volunteer works by his own free choice in favour of the community well-being. In this regard, Hasky-Leventhal *et al.* (2018) introduce the notion of "volunteerability", defining it as the individual's ability to overcome related obstacles and volunteer, and relating it with the concepts of willingness, capability and availability. Mulder *et al.* (2015) expanded the TSR literature by identifying a triadic relationship among volunteer, service provider and community to describe the transformative charitable experiences. However, in their article, the authors focalized the analysis mainly on the well-being generated for the volunteer, demonstrating how this actor is at the same time consumer and provider of the service in a charitable experience.

METHODOLOGY

The study was carried out in collaboration with the volunteering association Kinds Kicking Cancer (KKC) Italia. It was originally founded in United States in 1999 and in 2011 was established also in Italy. KKC Italia is a non-profit organization that helps children with cancer and severe chronic conditions and their families to cope and better manage the disease by teaching martial arts. These activities are developed with a supportive therapeutic aim to help patients in dealing with their illness. The association was selected because it operates with its co-therapy services in many Italian hospitals (i.e. Bambino Gesù, Policlinico Gemelli, Policlinico Umberto I, etc.) and multiple regions (i.e. Lazio, Campania, Umbria, Piedmont, Lombardy, etc.).

A qualitative study was carried out to describe and analyze the role of volunteers in the healthcare service ecosystems and how their value co-creation activities contribute to the well-being of the involved actors. A qualitative methodology is considered appropriate to study new and complex phenomena and to analyze individual's feelings about specific issues (McCusker and Gunaydin, 2015; Boulay *et al.*, 2014). The investigation was carried out integrating two methodological tools in-depth interview and diary analysis.

A total of 17 in-depth interviews were carried out at two different levels. Specifically, first the researchers carried out two in-depths interviews with the founder and the president of the association and five in depth interviews with the volunteers which manage the collaboration with hospitals. The objective of this phase was: i) to understand deeply the mission, the vision and the values of the association; ii) to get a clear picture of the activities carried out and comprehend the partnership process with hospitals; iii) to have a complete vision of the healthcare ecosystem with the involved actors and understand the volunteers' role; iv) to collect their perspective regarding the impacts of volunteering on the stakeholders' well-being. Then the authors performed 10 in-depths interviews with volunteers and analysis of one-year volunteer's diary to examine: i) the volunteer's works and responsibilities; ii) the volunteers' perception of the transformation generated on individuals and communities' well-being throughout the provision of co-therapy programs within hospitals; iii) the inner transformation and the effects on the volunteers' well-being. The interviews were carried out in November 2021.

Simultaneously, the authors coded and interpreted the diaries describing the volunteers' experiences during 2019 and in the second part of 2021. Due to the Covid-19 pandemic, the activities were postponed until the second part of 2021, hence it was not possible to collect further evidence during 2020. The diary is a research method that allows collecting in situ information from a large sample and data about daily activities, self-reflections, and opinions (Guglielmetti Mugion and Menicucci, 2020). The volunteer, at the end of each co-therapy experience, has to report out in a diary the following contents: general information (e.g. number of patients, names, age, and ward), activities performed (I.e. physical exercises, breathing technique and meditation), and emotions and feelings. These reports are collected by the association and shared with all the volunteers on a monthly base. Each monthly diary contains approximately 70 reports.

The transcription of the in-depth interviews and diaries were analyzed separately using a thematic analysis. In both the cases, the authors followed the six phases process identified by Braun and Clarke (2006). In the first, phase the researchers transcribed the interviews and collected the diaries. Each file was stored with name and date. During the second phase, the authors used the software MAXQDA Analytics Pro 2020 to manage and analyze the data. Multiple investigators were involved to guarantee the research rigor (Côté and

Turgeon, 2005; Lincoln and Guba, 1985). The recurring topics where counted and coded. Then, the researches started the phase “Searching for Themes”, by grouping relevant codes into themes (Braun and Clarke, 2006; Charmaz, 2001) considering the relevant literature on value co-creation activities implemented in the healthcare context (i.e. McColl-Kennedy *et al.*, 2012, Sweeney *et al.*, 2015; Lam and Bianchi, 2019). In the fourth phase, codes and themes were reviewed to verify their logical pattern and consistency with the research question. Afterward, authors assigned a name to each them, describing its content. Finally, in the “Producing the Report” phase a report was developed to depict findings and the final interpretation. To support the themes comprehension quotes from participants were reported (King, 2004). An example of the coding output process for diaries analysis is provided in Table 1, which include: the detected codes with their frequencies, the related identified final co-creation theme, the theme link to the literature, and finally, the description of the co-creation theme examined within the empirical context of volunteering in the healthcare sector.

Table 1: Example of Diaries coding process output

Codes	Frequencies	Final Theme	Theme Related literature	Description in context
Establish a contact	35	Connecting (co-created relationships)	*Mulder et al., 2015; Lam and Bianchi, (2019); McColl-Kennedy et al., (2012); Sweeney et al., (2015)*	Volunteers create relationships with all actors involved. Specifically, they need to engage with the young patients and their families to have the opportunity to carry out the activities and get positive results.
Encourage	25			

In the following section, the preliminary results of the ongoing analysis are presented.

RESULTS

This section presents the preliminary results of the in-depth interviews and the thematic analysis of the diaries. The analysis and results provided a basis for understanding how the association carry out co-therapy activities and the pivotal actors involved in the healthcare service ecosystem. In addition, the main volunteers' value co-creation activities are presented. Finally, the transformative outcomes in terms of well-being for all the involved actors are reported.

Generally, the volunteers attempt to build a connection with the young patients, and then they start the activity by practicing physical moves (when possible), breathing exercises and meditation practices helpful during painful therapies. In doing that, families are also involved in facilitating the patient's engagement and co-create shared moments of distraction and emotional well-being. From the volunteer's point of view, the activities allow the child to grow apart for a moment from the disease, and help him vent anger, have fun, relax, and manage pain. Moreover, activities can also positively impact family members who can participate in the activity together with children or take a moment for themselves and get away from the disease for a few minutes. Sometimes the volunteer must try to convince and stimulate the child to carry out activities because some patients may be reluctant. The parents could have an essential role in acting as an agent for setting the connection between the volunteer and the patient. On the other side, in some situations, the family may prevent the connection for fear or a sense of protection triggered by the vulnerability of children. In addition, The Covid-19 outbreak stopped activities that slowly resumed only in the second half of 2021 and in a partial manner. According to the volunteers, the pandemic waves negatively impacted patients who have been denied both the possibility of carrying out activities that amused and distracted them, and to which they were accustomed.

The actors involved in the co-therapy process can be grouped into four categories: the volunteers, the patients, their family and the hospital (including physicians, nurses, and administrative staff).

The investigation allowed the authors to understand the value co-creation activities performed by the volunteers and the potential effects on actors' well-being. In the diaries volunteers described their experience immediately after the activities and it allows researchers to collect more information about self-reflections and impressions going deeper in their instantaneous feelings. Simultaneously, the interviews put forward the possibility to go further in diaries results and add more data about volunteer's role and responsibilities, understand the drivers at the basis of volunteer's motivations and their perceptions of the generated well-being, even for them-self. After a first separate analysis, the authors examined together diaries and interviews results and to achieve the study objective and they identified the value co-creation activity's themes which are specific for volunteers in the healthcare ecosystem: *connecting, co-production, compliance with HSP requirements, manage patients and provide co-therapies*. The results are described in Table 2 and examples of quotes are used to support the understanding of the themes. Some of them were already recognized in literature as co-creation activities carried out by other stakeholders such as patients, families, customers (i.e. Mulder *et al.*, 2015; Lam and Bianchi, 2019; McColl-Kennedy *et al.*, 2012; Sweeney *et al.*, 2015) and the authors effort was to connect and interpret the literature examined in relation to the phenomenon under investigation and the specific actor.

Table 2: Volunteers' value co-creation activities

Volunteer's value co-creation activities	Description	Quotes
Connecting (co-created relationships)	Volunteers create relationships with all actors involved. Specifically, they need to engage with the young patients and their families to have the opportunity to carry out the activities and get positive results.	*"Initially the mother seems a bit uncertain, but we explain that the exercises can also be performed from the bed and so we start the activities with the ritual greeting".*
Co-production	Volunteers co-produce the activities in accordance with patients, families and HSP regulation which are all involved in the activity's implementation and design.	*"Fabio explains the importance of breathing exercises and the grandfather intervenes to tell us that he always tells him how useful and important it is to breathe".*
Compliance with HSP requirements	Volunteers must comply with the regulations communicated by the health facility regarding how to manage patients and how to use the spaces	*"The hospital provides us with directions and there are regulations that we must follow to get in touch with children, even more stringent during the covid-19"*
Manage patients and provide co-therapies	Volunteers help HSP to manage patients and they provide co-therapies that can help children deal with their illness.	*"For nurses it is difficult to manage patients all day and we help to do so, in addition children after activities are often more relaxed and happier and this is an additional help for health professionals".*

Moreover, based on respondent's point of view, authors highlighted the well-being dimensions which were impacted by the volunteers' value co-creation activities for the involved actors: patients (*emotional regulation, have fun*), families (*relax, positive thinking*) and volunteers (s*atisfaction and realization, empathy, burnout*) which are presented and depicted in Table 3. As previously, researchers started from categories already recognized in literature (i.e. Gross, 1999; Duhachek, 2005; Fagerlind *et al.*, 2010; Cordova *et al.*, 2003; Sweeney *et al.*, 2015; Mulder *et al.*, 2015; Mareike and Karsten, 2020; Watson *et al.*, 1998) linking them with the specific stakeholders of the current research, in this process the data reveal new well-being outcomes categories: relax (for families), burnout and empathy (for volunteers).

Table 3: Well-being outcome by actor

Actor	Well-being outcomes (volunteer's perspective)	Description	Quotes
Patients	Emotional regulation	Martial art therapy and volunteers' practices helps patients to cope with their emotions.	*"Alessandro began to laugh and seemed not to want to stop playing this game, his shots in the meantime had become so powerful that the shooter hit in sequence Roberto and me. Then he wanted to use the striker as a sword and threw himself into an epic battle".*
	Have fun	Participation in the exercises proposed by the volunteer allows children to have fun for a moment and forget the disease.	
Families	Relax	The intervention of the volunteer gives the possibility to the relatives to take some time for themselves and to have the possibility not to care for some moments the children.	*"In the final relaxation, aimed at removing the bad thoughts, even the mother falls asleep finding for a moment some peace".*
	Positive thinking	Seeing the child happy and amused allows the family member to develop a positive thinking that allows him to fight and better manage the disease.	
Volunteer	Satisfaction and realization	The volunteer feels satisfied and fulfilled when at the end of the activities with families and children he perceives that his intervention has allowed them to feel better, better manage the disease and have a little distraction.	*"I like to see the father's gloomy face lie down slowly and also the smile of the son".*
	Empathy	The experience allows volunteers to enhance their level of empathy.	*"Feelings are very strong and sometimes it is better to take breaks to overcome the negative feelings that you experience during volunteer activities".*
	Burnout (negative)	There is also a downside that volunteers can experience the burnout, determined by the inability to manage the strong emotions following volunteering.	

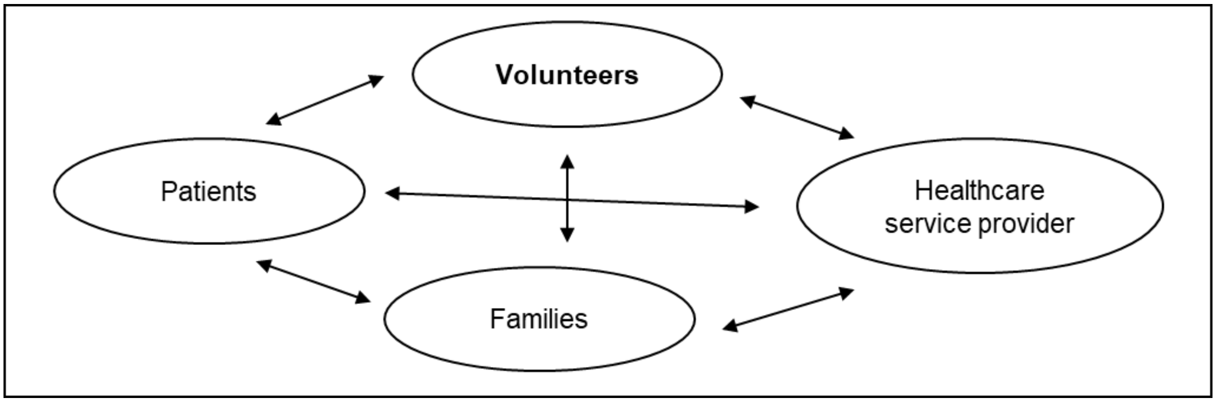
DISCUSSION

The presented preliminary results shed light on the essential role (tasks, activities, and outcomes) the volunteers play in the healthcare ecosystem.

The empirical results allow depicting the main actors involved in the value creation process of volunteering activities within the healthcare ecosystem: volunteers, volunteering associations, healthcare providers (including nurses, physicians, and no medical staff), patients and their families. It allows getting a picture of the healthcare service ecosystem (Figure 1) understanding how the volunteers are integrated into it. Specifically, the Mulder *et al.* (2015) framework is confirmed and adapted to the healthcare context, and an additional actor is included (families).

The empirical analysis, in addition, reveals that volunteers' activities contribute to co-create transformative value not only for the patients, instead generating well-being outcomes for all the actors involved. Mainly, combining existing literature and the results of the qualitative data analysis, four main categories of value co-creation depicted are: connecting (co-created relationships) (Mulder *et al.*, 2015; Lam and Bianchi, 2019; McColl-Kennedy *et al.*, 2012; Sweeney *et al.*, 2015), co-production (Lam and Bianchi, 2019; McColl-Kennedy *et al.*, 2012; Sweeney *et al.*, (2015), compliance with HSP requirements (Sweeney *et al.*, 2015), and manage patients and provide co-therapies (Mulder *et al.*, 2015; Guglielmetti Mugion and Menicucci, 2020).

Figure 1: Simplified representation of the Healthcare ecosystem and volunteering value creation process.



As pointed out by different authors, TSR is grounded on interactions characterized by collaboration, respect, and sustainability improvement (Mulder *et al.*, 2015; Rosenbaum *et al.*, 2011). In line with this perspective, this research allows pointing out that the co-therapy activities performed by volunteers within hospitals

generate transformative value for the healthcare ecosystem, namely to create well-being outcomes at both individual and community levels. This is enabled by the active collaboration of all the involved actors that cooperate to create value for the whole ecosystem.

In addition, the present research, not only confirmed that volunteers while operating create well-being for themselves ("volunteers may be served while serving", Mulder *et al.* 2015, p.877), but also identified the well-being outcomes generated by the volunteering activities for each category of actors operating in the ecosystem. For patients, *emotional regulation* and *having fun* are created (Gross 1999; Duhachek 2005; Fagerlind *et al.*, 2010; Cordova *et al.*, 2003; Sweeney *et al.*, 2015), while for their family *relax* and *positive thinking* are generated (Duhachek 2005; Fagerlind *et al.*, 2010; Cordova *et al.*, 2003; Sweeney *et al.*, 2015). Volunteers' well-being outcomes refer to *satisfaction*, *realization*, and *empathy*, but can also produce some adverse effects in terms of burnout (Mulder *et al.*, 2015; Mareike and Karsten, 2020; Watson *et al.*, 1998). For the hospitals and their staff, well-being outcomes are linked with a more well-structured organization of the entertainment of patients and their family which translates into a *better relationship* with the patient and, accordingly, a greater *staff satisfaction*.

Co-therapy services provided by volunteers and charitable organizations within the hospital helps to increase the well-being of the patients and allow extending the creation of transformative value for other actors involved and for the community in general. This is in line with the Gallan *et al.* (2019) study that pointed out the importance of connecting patients' ecosystems with those of others to contribute broadly to the community well-being. In addition, the volunteer throughout is activities allows *putting humans first* (Field *et al.*, 2021) into the healthcare ecosystem, developing trust, agility and resilience.

CONCLUSION

The aim of this paper is to identify the main categories of actors interacting with the volunteers in the value creation process and describe how the volunteers co-create transformative value by exchanging resources with the other actors. Finally, the article presents the analyse of the well-being outcomes for each category of actor involved.

This paper is one of the few to investigate the transformative phenomenon and the mechanism and outcome of value co-creation during volunteer activities in the healthcare context. Negative and positive impacts on the individual and collective well-being of involved stakeholders were highlighted. Indeed, the study contributes to the current knowledge, providing valuable insights into transformative value co-creation practices and related well-being in the healthcare sector. It highlights the pivotal role of volunteers and co-therapy services in triggering resources exchanging practices that generate well-being not only for patients but also for all the categories of actors. Accordingly, the present research attempts to provide empirical evidence to enrich the services research priorities identified by relevant authors (i.e. Field *et al.* 2021; Rosenbaum, 2015; Ostrom *et al.* 2015; Baron, Warnaby and Hunter-Jones, 2014; Ostrom *et al.* 2010) by advancing theories related to both TSR and sustainable service ecosystem.

The empirical analysis provides practical implications, generating beneficial implications for multiple actors. The role of volunteers and volunteering organizations in the healthcare ecosystem is recognized, and the transformative value co-creation practices are bought to the light. In addition, hospitals, healthcare service providers, and charitable organizations have access to evidence-based information to improve co-therapy and design new services to increase the patients' well-being.

Since the empirical case and qualitative data collected refer only to a volunteering association (KKC Italia) and its volunteers, the results could be affected by some bias related to the specific co-therapy activity performed (martial art therapy). Future studies may be carried out to confirm or extend the presented outcomes by including different co-therapy activities (e.g. horticultural, ceramic, etc.). In addition, the present research is contextualized in Italy, and it may be interesting to develop cross-country comparative research aimed to investigate how the social context and the institutional arrangement can affect both the co-creation practices and the well-being outcomes.

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Meditation reduces brain activity in the default mode network in children with active cancer and survivors

Aneesh Hehr[1] | Allesandra S. Iadipaolo[2] | Austin Morales[1] | Cindy Cohen[3] | Jeffrey W. Taub[4,5] | Felicity W. K. Harper[6,7] | Elimelech Goldberg[7] | Martin H. Bluth[3,8,9] | Christine A. Rabinak[1,2,10] | Hilary A. Marusak[1,6,10]

[1]Department of Psychiatry & Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, Michigan, USA

[2]Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA

[3]Kids Kicking Cancer, Southfield, Michigan, USA

[4]Department of Pediatrics, Wayne State University, Detroit, Michigan, USA

[5]Children's Hospital of Michigan, Detroit, Michigan, USA

[6]Karmanos Cancer Institute, Detroit, Michigan, USA

[7]Department of Oncology, Wayne State University, Detroit, Michigan, USA

[8]Department of Pathology, School of Medicine, Wayne State University, Detroit, Michigan, USA

[9]Department of Pathology, Maimonides Medical Center, Brooklyn, New York, USA

[10]Merrill Palmer Skillman Institute for Child and Family Development, Wayne State University, Detroit, Michigan, USA

Correspondence
Hilary Marusak, 3901 Chrysler Service Dr, Suite 2B, Detroit, MI 48201, USA.
Email: hmarusak@med.wayne.edu

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Abstract

Background: Mounting evidence demonstrates that meditation can lower pain and emotional distress in adults, and more recently, in children. Children may benefit from meditation given its accessibility across a variety of settings (e.g., surgical preparation). Recent neuroimaging studies in adults suggest that meditation techniques are neurobiologically distinct from other forms of emotion regulation, such as distraction, that rely on prefrontal control mechanisms, which are underdeveloped in youth. Rather, meditation techniques may not rely on "top-down" prefrontal control and may therefore be utilized across the lifespan.

Procedure: We examined neural activation in children with cancer, a potentially distressing diagnosis. During neuroimaging, children viewed distress-inducing video clips while using martial arts-based meditation (focused attention, mindful acceptance) or non-meditation (distraction) emotion regulation techniques. In a third condition (control), participants passively viewed the video clip.

Results: We found that meditation techniques were associated with lower activation in default mode network (DMN) regions, including the medial frontal cortex, precuneus, and posterior cingulate cortex, compared to the control condition. Additionally, we

Abbreviations: ACCEPT, mindful acceptance; BOLD, blood oxygen level-dependent; BREATH, focused attention to breath; CAMM, Child and Adolescent Mindfulness Measure; CEN, central executive network; DISTRACT, distraction; DMN, default mode network; fMRI, functional magnetic resonance imaging; FWE, familywise error; LOOK, passive viewing; MFC, medial frontal cortex; MNI, Montreal Neurological Institute; SCARED, Screen for Child Anxiety-Related Emotional Disorders; VAS, visual analog scale.

found evidence that meditation techniques may be more effective for modulating DMN activity than distraction. There were no differences in self-reported distress ratings between conditions.

Conclusion: Together, these findings suggest that martial arts-based meditation modulates negative self-referential processing associated with the DMN, and may have implications for the management of pediatric pain and negative emotion.

KEYWORDS

adolescents, functional magnetic resonance imaging, martial arts, mindfulness

1 | INTRODUCTION

The ability to regulate emotion develops across the first two decades of life, corresponding with maturational changes in brain networks supporting emotion processing and self-regulation.[1] Emotion regulation is central to developmental outcomes.[2–4] Deficits in emotion regulation can increase risk of mental disorders in adulthood (e.g., depression).[5] Therefore, strategies that are effective for bolstering emotion regulation during childhood may have long-term benefits, such as ameliorating adverse outcomes during adulthood.[6]

Emotion regulation strategies that involve forms of *mindfulness and meditation* originate from ancient practices.[7] Meditation refers to an umbrella of mental practices that involve the monitoring and regulation of attention and emotion.[8,9] Mindfulness is a form of meditation that involves focusing attention to and accepting thoughts and emotions in the present.[10] There are also individual differences in the tendency toward mindfulness (i.e., trait mindfulness) that can change over time through deliberate meditation practice.[11] Trait mindfulness is defined as an individual's innate ability to maintain attention to the present moment and is thought to be a critical factor contributing to overall psychological health.[12–14] Trait mindfulness is also relevant for meditation-based interventions, wherein individuals with high levels of trait mindfulness at baseline may be more responsive to interventions.[9] State mindfulness, on the other hand, refers to more transient or temporary periods of mindfulness.[9] Repeated practices of mindful states may induce more stable or trait-level changes in mindfulness.[15] Meditation techniques are now integrated into established treatments for psychological disorders involving emotion dysregulation, including depression.[16] Meditation programs have been shown to be effective for reducing stress, anxiety, depression, and pain among clinical[17] and nonclinical[18] adult populations. They show promise for reducing disease- and treatment-related distress among patients with chronic conditions, such as cancer.[19] Active engagement in meditation has also been shown to lower self-reported pain and negative emotion.[20,21]

Although most research has been conducted in adults, emerging evidence suggests that mindfulness and meditation are beneficial for children. A meta-analysis of 33 randomized controlled trials reported benefits of meditation programs on attention, depression, and stress among clinical and nonclinical pediatric samples.[22] Mindfulness and meditation-based programs are popular in school settings,[23] and increasingly used to help children cope with stressful experiences, such as chronic conditions (e.g., cancer)[24,25] or trauma.[26] Meditation as an emotion regulation strategy is promising for preventing mental disorders, given that nearly half of all mental disorders begin during childhood and adolescence.[27] However, the neural mechanisms supporting meditation as an emotion regulation strategy in children remain unclear. Insight on these mechanisms could help validate and improve interventions for at-risk pediatric populations exposed to high stress and trauma.

Meditation strategies are distinct from other forms of emotion regulation, such as distraction. Rather than controlling attention away from emotional experiences, meditation strategies involve noticing and accepting emotional reactions as they arise.[8] Meditation also appears to be neurobiologically distinct from other forms of emotion regulation that rely on "top-down" (i.e., prefrontal-based) modulation of emotional responses. These forms of emotion regulation, such as distraction, commonly engage brain regions in the central executive network (CEN), including regions of the prefrontal cortex.[28,29] Meditation emotion regulation strategies do not appear to engage the CEN. Rather, these techniques have been shown to reduce activation in regions of the default mode network (DMN), including medial frontal cortex (MFC) and precuneus/posterior cingulate cortex, during deliberate meditation and exposure to aversive stimuli.[20,21,30] The DMN is associated with self-referential thought and depressive rumination.[31,32] Prior research suggests that individuals with depression fail to downregulate DMN activity when exposed to negative emotional stimuli.[33] Taken together, existing research suggests that meditation can modulate DMN activity, and these effects do not rely on prefrontal-based control mechanisms. This is important because children might not be able to employ complex regulatory strategies due to underdevelopment of the CEN.[34,35] Further, simple meditation strategies, such as focused attention to the breath, may be more accessible to children in stressful situations.

To our knowledge, only two functional magnetic resonance imaging (fMRI) studies have examined the neural correlates of meditation training in children. These studies report lower amygdala response to fearful faces and lower resting-state functional connectivity between the DMN and CEN in children (mean age = 11.75 years) following an 8-week mindfulness-based school program relative to a control computer programming course.[36,37] These finding support the notion that meditation can modulate brain activity (e.g., DMN) in children. These patterns are consistent with our prior fMRI study showing that more trait mindful youth spent less time in a dynamic functional connectivity state characterized by higher DMN–CEN connectivity.[38] However, no studies to our knowledge have examined neural activity in children actively engaged in meditation emotion regulation.

To address this gap, we examined the within-subject effects of meditation on brain activity in a sample of children with cancer, who may be prone to experiencing significant disease- and treatment-related distress.[39] Participants received minimal meditation training (4 hours) through a well-established martial arts-based meditation program[24,25] prior to undergoing an adapted version of an established fMRI emotion regulation task in the scanner. The 4-hour minimum was to improve feasibility and fidelity to the mindfulness conditions during scanning. Our goal was to ensure that participants were able to reliably enter and maintain a mindful state at the time of scanning, so that brain responses were robust. We compared two meditation emotion regulation techniques (i.e., focused attention and mindful acceptance) with a control condition (i.e., passive viewing) and with a non-meditation emotion technique (i.e., distraction). Participants were asked to engage in one of the four conditions while they were exposed to aversive video clips (e.g., a child receiving an injection), and rated their negative emotion after each trial. This design allowed us to test (a) whether meditation techniques can reduce brain activity in the DMN, and (b) whether meditation emotion regulation techniques are more effective than a non-meditation technique (distraction) at reducing DMN activity. We also (c) compared brain activation during the two meditation techniques, based on evidence that different meditation techniques have different effects on brain activity.[40]

2 | MATERIALS AND METHODS

2.1 | Participants

This preliminary study reports on 12 childhood cancer patients or survivors (ages 5–17 years; five female) recruited from the Children's Hospital of Michigan Hematology/Oncology clinic (Detroit, MI, USA) and from local cancer support groups and organizations (e.g., Kids Kicking Cancer, Gilda's Club of Metro Detroit). Data were collected from August 2017 through January 2019 as part of a larger prospective study examining the effects of a martial arts-based program, Kids Kicking Cancer (www.kidskickingcancer.org), on pain, emotional distress, and health-related quality of life among children with cancer (Supporting Information). Eligible participants were ages 5–17 (inclusive), English-speaking, and previously diagnosed with any form of pediatric cancer that did not include the central nervous system. Youth were excluded if they had MRI contraindications (e.g., claustrophobia, braces, non-MRI compatible port), major sensory impairments (e.g., severe vision loss), comorbid neurological disorders (e.g., epilepsy), gross neuropathologies (e.g., ventriculomegaly), pervasive developmental disorders, or other severe psychopathology (e.g., schizophrenia). The study was approved by the Wayne State University Institutional Review Board. Written informed consent and assent were obtained from participating primary caregivers (i.e., parent or legal guardian) and youth, respectively. Participant demographics and clinical characteristics are provided in Table 1.

2.2 | Questionnaire measures

Prior to the MRI scan, youth were assisted by a trained member of the research staff in completing standardized self-report measures of anxiety and trait mindfulness.

2.2.1 | Anxiety symptoms

Anxiety symptoms were measured using the 41-item Screen for Child Anxiety-Related Emotional Disorders (SCARED)[41] that shows good reliability, as measured via internal consistency and test–retest reliability. The SCARED demonstrates good discriminative validity between anxiety and non-anxiety disorders.[42,43] Total possible SCARED scores range from 0 to 82, with scores of ≥25 recommended for differentiating anxious from nonanxious youth, and may indicate the presence of an anxiety disorder.[44] In the present sample, 25% ($n = 3$) of participants exceeded this threshold for detecting potential anxiety.

2.2.2 | Trait mindfulness

Youth completed the Child and Adolescent Mindfulness Measure (CAMM), a 10-item measure of trait mindfulness.[14] Possible scores range from 0 to 40, with higher scores indicating higher mindfulness. The CAMM shows adequate internal consistency (Cronbach's alpha = .81–.88), reliability, and validity in youth samples.[13,14] Here, we report trait mindfulness in our participants, as trait mindfulness is thought to be relevant for responses to meditation-based interventions and predicts overall psychological health.[9] We explored whether trait mindfulness was associated with neural activity. Although we ask participants to go into a transient mindful *state* during the scan, capturing state mindfulness during the task would have interfered with task demands.

2.3 | Emotion regulation task

Participants completed an adapted emotion regulation task[45,46] during fMRI scanning. During the task (Figure 1), participants viewed distress-inducing stimuli and rated their current emotional distress after each trial. Participants rated their distress on a 1–6 visual analog scale (VAS; 1 = "No distress at all," 6 = "Worst possible distress") using an adapted version of the FACES scale.[47,48] The FACES scale was previously adapted by Trentacosta and colleagues to capture emotional distress related to children's cancer treatments, rather than pain levels.[47] We used the adapted version here, given our interest in

TABLE 1 Participant demographics and clinical characteristics

Variable	*n* (%)	*M* (SD)	Range
Age (years)		10.33 (3.26)	5–17
Age at diagnosis (years)		5.48 (4.49)	1–17
Biological sex (females)	5 (42%)		
Length of treatment (years)		3.06 (0.73)	2–4
Cancer diagnosis			
Acute lymphoblastic leukemia (ALL)	8 (67%)		
Acute promyelocytic leukemia (APML)	1 (8%)		
Neuroblastoma	1 (8%)		
Wilms tumor	1 (8%)		
Juvenile myelomonocytic leukemia	1 (8%)		
Active cancer patients	5 (41.7%)		
Types of treatment			
Chemotherapy	11 (91.7%)		
Surgery	3 (25%)		
Radiation	1 (8.3%)		
Blood transfusion	1 (8.3%)		
Bone marrow transplant	1 (8.3%)		
Approximate time since last treatment, in years (survivors)		3.4 (1.8)	1–5
Race/ethnicity			
White, non-Hispanic	7 (58.3%)		
African American, non-Hispanic	3 (25.1%)		
Other	1 (8.3%)		
Not reported	1 (8.3%)		
Annual household income			
$0–10,000	1 (8.3%)		
$10,000–20,000	1 (8.3%)		
$20,000–30,000	2 (16.7%)		
$30,000–40,000	1 (8.3%)		
$40,000–50,000	1 (8.3%)		
$50,000–60,000	0 (0%)		
$60,000–80,000	3 (25%)		
$80,000–100,000	1 (8.3%)		
$100,000–120,000	0 (0%)		
$120,000–140,000	1 (8.3%)		
Not reported	1 (8.3%)		
Trait mindfulness (CAMM)		30 (10.4)	3–40
Anxiety symptoms (SCARED)		25.6 (17.7)	6–60

Abbreviations: CAMM, Child and Adolescent Mindfulness Measure; SCARED, Screen for Child Anxiety-Related Emotional Disorders.

emotion regulation. Task stimuli consisted of 10 validated 30-second video clip vignettes depicting various realistic, salient stressors (e.g., child receiving an injection) that have been shown to induce transient distress in children.[49] Negative stimuli were used to test for differences in brain response to distress-inducing stimuli. Participants were explicitly instructed to pay attention to the movie as if it were real, pretend they were the child in the movie, and react as if they were in that situation. Prior to each video clip, participants were given instructions for one of four conditions: (a) focused attention to breath, BREATH; (b) mindful acceptance, ACCEPT; (c) distraction, DISTRACT; or (d) passive viewing, LOOK. During BREATH, participants were instructed to focus their attention on their breathing in a

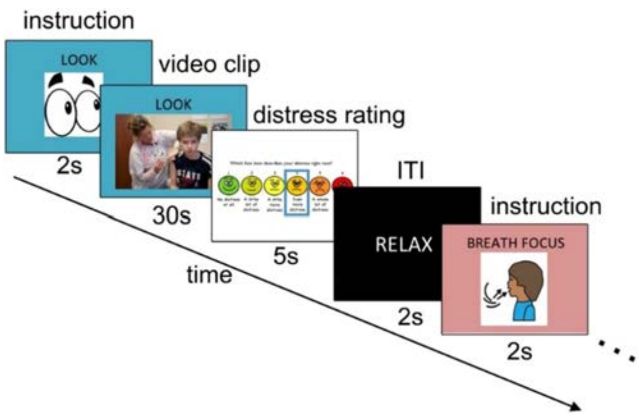

FIGURE 1 Emotion regulation task. Participants received one of four instructions prior to watching the video clip. After each clip, participants rated their level of distress (1 = no distress at all, 6 = the worst possible distress) on a visual analog scale (VAS), which is an adapted version of the Wong and Baker's FACES scale. Instructions consisted of (i) LOOK, a control condition during which participants were instructed to passively view the video clip; (ii) DISTRACT, a non-meditation condition during which participants were instructed to count backwards from 10; and two meditation emotion regulation techniques: (iii) BREATH, during which participants were instructed to focus their attention on their breathing in a nonjudgmental context; and (iv) ACCEPT, during which participants were instructed to pay attention, in a nonjudgmental manner, to the emotions they were experiencing and accept them

nonjudgmental manner, and during ACCEPT, participants were instructed to pay attention to the emotions they were experiencing and just accept (or "be okay with") them. During DISTRACT, participants were instructed to count backwards from 10 in their head. DISTRACT was selected as the non-meditation emotion regulation technique, because distraction is the most commonly used technique to manage children's pain and distress in clinical settings.[4] DISTRACT differs from BREATH in that DISTRACT involves directing attention away from emotional experiences, whereas BREATH involves noticing and accepting emotional reactions and focusing on an internal sensation (the breath) in a non-judgmental manner. During the control condition, LOOK, participants were instructed to passively view (or "just watch") the video clip. More details about how these were instructed in class and during the pre-scan mock scanner training session are provided in the Supporting Information. Participants were cued using the text and visual cue during the task in the fMRI scanner. Each trial lasted 37 seconds, and included a 2-second instruction slide, a 30-second video clip, and a 5-second emotion rating period (Figure 1). The inter-trial interval (2 seconds) was a "RELAX" screen. There were five trials of each of the four conditions, for a total of 20 trials (total time = 13 minutes 21 seconds). Video clips were counterbalanced across conditions. Presentation software (Neurobehavioral Systems, Inc.) was used for stimulus presentation and behavioral data acquisition. The task was displayed on a back-projection screen affixed to the head coil and behavioral responses were registered using a 2×2 MR-compatible response device.

2.4 | Emotional distress ratings

Distress ratings were averaged for each condition (BREATH, ACCEPT, DISTRACT, LOOK) and submitted to IBM SPSS software v.26 for within-subject analysis. Overall effects of condition were examined using a one-way nonparametric Friedman test for repeated measures ($p < .05$). Post hoc repeated measures Wilcoxon signed-ranks tests were used to further examine differences in distress ratings between conditions. Behavioral data were missing for one subject due to errors in data collection.

2.5 | fMRI data acquisition and analysis

Details regarding blood oxygen level-dependent (BOLD) imaging fMRI data acquisition, preprocessing, quality assurance, and first-level analyses are provided in the Supporting Methods.

2.5.1 | Second-level analysis

Group-level random effects analysis was performed in SPM8 to examine within-subjects differential activation patterns based on instruction, using one-sample *t*-tests. First, to identify regions modulated by meditation emotion regulation techniques versus a control condition, we examined the contrasts BREATH versus LOOK and ACCEPT versus LOOK. To identify regions modulated by the non-meditation emotion regulation condition, we examined DISTRACT versus LOOK. Then, we compared the two meditation conditions (BREATH vs. ACCEPT) and compared the meditation versus non-meditation instructions (i.e., BREATH vs. DISTRACT, ACCEPT vs. DISTRACT).

2.5.2 | DMN analyses

To identify the effects of different emotion regulation techniques on brain activity, we focused on a priori regions of interest in the DMN: MFC, posterior cingulate cortex, dorsal frontal cortex, and supplementary motor area. Small-volume familywise error (FWE) correction was used to identify significant results ($p_{FWE} \leq .05$ and five-voxel minimum).

2.5.3 | Whole-brain analyses

A complementary whole-brain analysis was performed using a whole-brain FEW-corrected threshold ($p_{FWE} < .05$). See Supporting Information for details.

2.5.4 | Exploratory analyses

Of note, although our sample consisted of patients undergoing active treatments and survivors, our main focus was on within-subjects effects. We did not perform between-subjects analyses given the relatively limited sample size and the potential confounding factors between groups. However, we did explore associations with age (older vs. younger, median split), anxiety symptoms (SCARED scores, continuous), and trait mindfulness (CAMM scores, continuous).

3 | RESULTS

3.1 | Distress ratings

There was no main effect of condition (BREATH, ACCEPT, DISTRACT, LOOK) on distress ratings following negative video clips, Friedman's two-way analysis of variance by ranks, df = 3, test stat = 2.35, p = 0.5 (Supporting Information, Table S1). Post hoc repeated measures Wilcoxon signed-ranks tests also revealed no significant differences between conditions; $p > .1$.

3.2 | fMRI results

3.2.1 | Effects of meditation emotion regulation strategies (vs. passive viewing)

A whole-brain BREATH versus LOOK contrast revealed lower activity in several regions of the DMN, including the precuneus, parahippocampal gyrus, and posterior cingulate cortex, and also the cuneus and lingual gyrus (Table 2, Figure 2B). There were no regions showing the opposite pattern (i.e., higher activity for BREATH relative to LOOK; Table 2) and no significant effects for the BREATH versus LOOK contrast in any DMN region (p_{FWE} > .05). There were also no significant effects for the ACCEPT versus LOOK contrast at the whole-brain threshold (Table 2) or in any DMN region (p_{FWE} > .05).

3.2.2 | Effects of a non-meditation emotion regulation strategy (vs. passive viewing)

There were no significant effects for the DISTRACT versus LOOK contrast at the whole-brain threshold (Table 2) or in any DMN region (p_{FWE} > .05).

3.2.3 | Comparison between meditation emotion regulation strategies

Region-of-interest analyses showed differential DMN activity for the BREATH versus ACCEPT contrast in the MFC, such that MFC activation was lower during the BREATH relative to the ACCEPT condition (xyz = 0, 58, 18, 9 voxels, Z = 3.73, p_{FWE} = .02; Figure 3A). No other regions were significant for the BREATH versus ACCEPT contrast, and there were no significant results for this contrast at the whole-brain corrected threshold (Table 3).

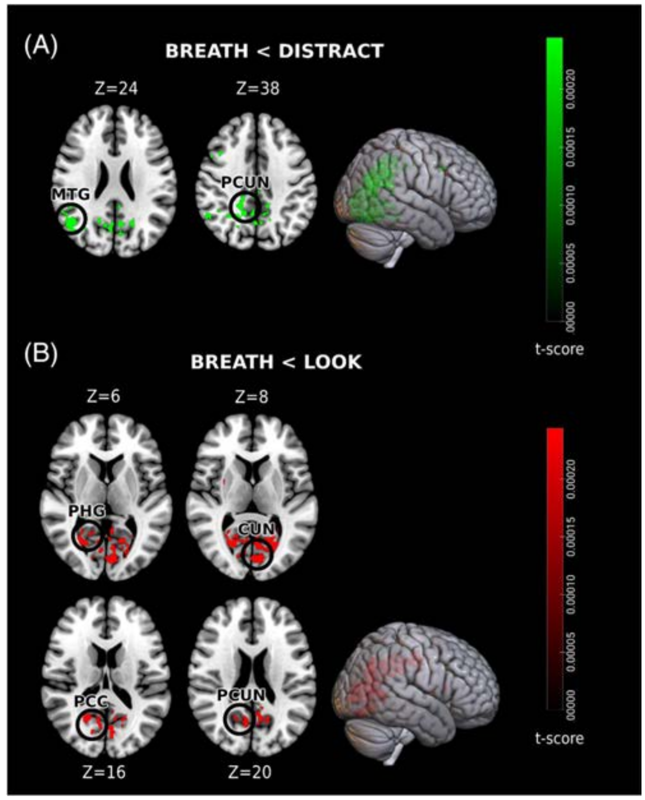

FIGURE 2 Whole-brain results. Effects of meditation emotion regulation techniques on activation in the default mode network (DMN). (A) Differential DMN activation associated with meditation (BREATH) versus non-meditation (DISTRACT) instructions. Green colors indicate lower BOLD response in the DMN for BREATH versus DISTRACT. (B) Differential DMN activation during meditation instructions (BREATH) versus a control condition (LOOK). Red colors indicate lower DMN activation during meditation instructions (BREATH) relative to a control condition (LOOK). Results significant at whole-brain threshold ($p < .001$, >6 voxels) and shown at $p < .005$ for display purposes. BOLD, blood oxygen level-dependent; CUN, cuneus; MTG, middle temporal gyrus; PHG, parahippocampal gyrus; PCG, posterior cingulate cortex; PCUN, precuneus. x, y, and z are Montreal Neurological Institute (MNI) peak coordinates

3.2.4 | Comparison between meditation and non-meditation emotion regulation strategies

A whole-brain BREATH versus DISTRACT contrast revealed lower activation in the precuneus and middle temporal gyrus at the whole-brain corrected threshold (Figure 2A, Table 3). No region showed significant activation for the BREATH versus DISTRACT contrast. For the ACCEPT versus DISTRACT contrast, there was lower DMN activation in the MFC (xyz = 2, 48, 22, 6 voxels, Z = 3.5, p_{FWE} = .05; Figure 3B). No other regions were significant for the ACCEPT versus DISTRACT contrast, and there were no significant clusters for this contrast at the whole-brain threshold (Table 3).

TABLE 2 Whole-brain results for regions showing differential activation while participants are engaged in meditation and non-meditation emotion regulation techniques versus the control condition

Regions of activation	BA	Laterality	*x*	*y*	*z*	Voxel extent (k_e)	*Z*-score
Meditation techniques (ACCEPT, BREATH) vs. the control condition (LOOK)							
LOOK > BREATH							
Cuneus	17		0	−80	8	32	3.64
Posterior cingulate cortex	30	R	20	−66	8	17	3.59
Posterior cingulate cortex	30	R	8	−64	10	16	3.45
Posterior cingulate cortex	30	L	−22	−68	8	13	3.44
Parahippocampal gyrus	30	R	28	−56	6	12	3.58
Posterior cingulate cortex	30	R	18	−58	16	11	3.81
Lingual gyrus	18	R	8	−70	2	10	3.64
Precuneus	31	R	6	−66	20	6	3.37
LOOK < BREATH: no significant clusters							
LOOK > ACCEPT: no significant clusters							
LOOK < ACCEPT: no significant clusters							
Non-meditation technique (DISTRACT) vs. the control condition (LOOK)							
LOOK > DISTRACT: no significant clusters							
LOOK < DISTRACT: no significant clusters							

Note: BREATH = focus attention to the breath in a nonjudgmental context; ACCEPT = pay attention to emotions in a nonjudgmental way; DISTRACT = count backwards from 10; LOOK = passively view the movie. *x*, *y*, and *z* are Montreal Neurological Institute (MNI) peak coordinates. Voxel extent refers to the spatial extent of each cluster. *R*/*L* refers to lateralization of activation. Results are corrected at the whole-brain level (voxelwise $p < .001$; cluster extent = 6 voxels).
Abbreviations: BA, Brodmann area; BOLD, blood oxygen level-dependent; N/A, not applicable.

TABLE 3 Whole-brain results for regions showing differential activation during different types of emotion regulation techniques (i.e., BREATH vs. ACCEPT vs. DISTRACT)

Regions of activation	BA	Laterality	*x*	*y*	*z*	Voxel extent (k_e)	*Z*-score
Comparison between meditation techniques (BREATH vs. ACCEPT)							
BREATH > ACCEPT: no significant clusters							
BREATH<ACCEPT: no significant clusters							
Comparison between meditation and non-meditation techniques (BREATH vs. DISTRACT, ACCEPT vs. DISTRACT)							
BREATH > DISTRACT: no significant clusters							
BREATH < DISTRACT							
Middle temporal gyrus	39	R	46	−66	24	53	3.32
Precuneus	31	R	12	−50	38	9	3.52
ACCEPT > DISTRACT: no significant clusters							
ACCEPT < DISTRACT: no significant clusters							

Note: ACCEPT, pay attention to emotions in a nonjudgmental way; BREATH, focus attention to the breath in a nonjudgmental context; DISTRACT, count backwards from 10; LOOK, passively view the movie. *x*, *y*, and *z* are MNI peak coordinates. Voxel extent refers to the spatial extent of each cluster. *R*/*L* refers to lateralization of activation. Results are corrected at the whole-brain level (voxelwise $p < .001$; cluster extent = 6 voxels).
Abbreviations: BA, Brodmann area; BOLD, blood oxygen level-dependent; N/A, not applicable.

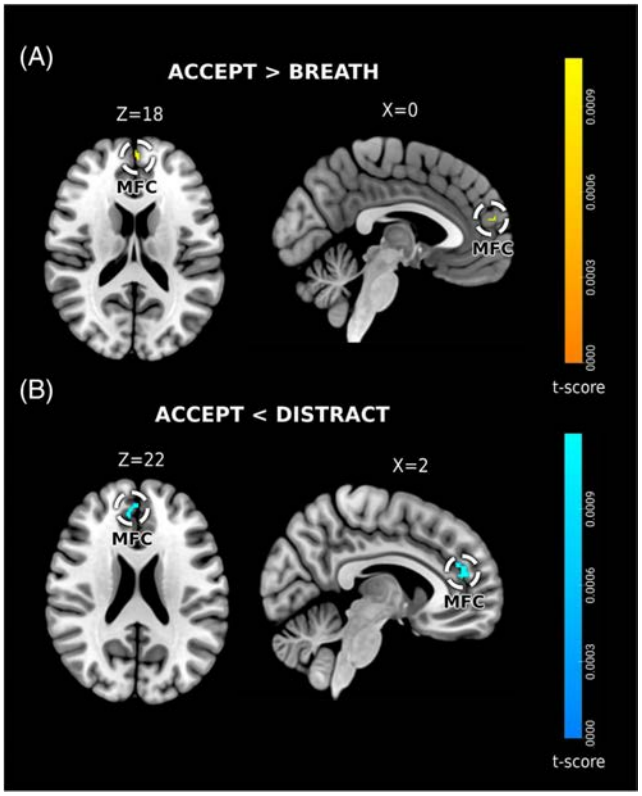

FIGURE 3 Region-of-interest results. Effects of meditation emotion regulation techniques on activation in the default mode network (DMN). (A) Differential DMN activation associated with ACCEPT versus BREATH meditation instructions. Yellow colors indicate greater BOLD response in the DMN for ACCEPT versus BREATH. (B) Differential DMN activation during meditation instructions (ACCEPT) versus non-meditation instructions (DISTRACT). Blue colors indicate lower DMN activation during meditation instructions (ACCEPT) relative to non-meditation instructions (DISTRACT). Results significant at small-volume-corrected threshfold ($p_{FWE} \leq .05$, >5 voxels) and shown at $p < .005$ for display purposes. BOLD, blood oxygen level-dependent; MFC, medial frontal cortex. *x*, *y*, and *z* are MNI peak coordinates

3.3 | Exploratory analyses

3.3.1 | Associations between brain activation and distress ratings

Distress ratings were not significantly associated with activation in any brain region that showed significant results in whole-brain or region-of-interest analyses ($p > .05$).

3.3.2 | Associations between distress ratings and demographic or clinical measures

Spearman correlation indicated that older age at diagnosis was associated with lower self-reported distress following the DISTRACT condition; $r(10) = -.75$, $p = .013$. Distress ratings were not associated with age, anxiety symptoms, nor trait mindfulness ($p > .05$). These findings remained nonsignificant after controlling for age at diagnosis ($p > .05$).

3.3.3 | Associations between brain activation and demographic or clinical measures

Activity in the DMN was not associated with age at diagnosis, anxiety symptoms, or trait mindfulness ($p > .05$). However, older children demonstrated lower brain activation in the posterior cingulate cortex (*xyz* = −22, −68, 8) during the BREATH versus LOOK contrast as compared to younger children; $r(12) = -.58$, $p = .049$. Older children also displayed lower activation in the middle temporal gyrus during the BREATH versus DISTRACT contrast than younger children; $r(12) = -.62$, $p = .032$. Controlling for age at the time of the scan, participants who were diagnosed at an older age showed higher brain activation in the middle temporal gyrus during the BREATH versus DISTRACT contrast, as compared to children who were diagnosed at a younger age; $r = .74$, $p = .035$.

4 | DISCUSSION

This is the first study, to our knowledge, to investigate the neural correlates of active meditation as an emotion regulation technique in a pediatric sample. We examined within-subjects differences in neural activation in children with cancer while they viewed distress-inducing video clips and engaged in meditation (focused attention, mindful acceptance) or non-meditation (distraction) emotion regulation techniques. In the control condition, participants passively viewed the video clip. The following findings emerged: (a) compared to the control condition, mediation emotion regulation techniques were associated with lower activity in several regions of DMN. (b) The non-meditation condition, distraction, was not associated with a similar reduction in neural activation as compared to the control condition, suggesting that meditation emotion regulation techniques may be more effective for downregulating DMN activity. (c) Meditation emotion regulation strategies were associated with lower DMN activity than distraction. Distraction is often used to manage children's pain in clinical settings (e.g., needle-related procedures).[50] Although there were no differences in distress ratings between conditions, evidence that meditation emotion regulation is more effective at quelling DMN activity may suggest longer term benefits—a hypothesis that requires future study with larger sample sizes. These findings may have implications for understanding the neural mechanisms underlying meditation-based emotion regulation in children.

Both forms of meditation emotion regulation strategies examined in this study were associated with lower activity in DMN regions, including the parahippocampal gyrus, precuneus, and posterior cingulate cortex. Lower activity in DMN during active meditation is consistent with prior fMRI studies in adults. For example, a meta-analysis of 78 fMRI studies in adults revealed consistent deactivations in

DMN regions (e.g., posterior cingulate cortex) during focused attention meditation.[40] Another fMRI study in meditation-naïve adults reported that mindful acceptance emotion regulation reduced pain-related activation in the DMN (e.g., posterior cingulate, precuneus).[20] We did not detect activation in the CEN during meditation, consistent with studies showing that meditation does not engage CEN control systems.[51] We also did not observe CEN activation for distraction, which may reflect underdevelopment of prefrontal-based forms of emotion regulation and the CEN.[34,35]

Our whole-brain and region-of-interest analyses revealed lower DMN activation for meditation emotion regulation techniques, but not for distraction. Prior studies on more prefrontal-based forms of emotion regulation (e.g., distraction) did not consistently report activation changes in the DMN,[51,52] and there is evidence that function of the DMN changes across development.[34] Distraction is considered an attention deployment strategy that redirects attention *away from* emotion-eliciting stimuli[53] and engages the CEN in adults.[51] Here, both meditation techniques (focused attention, mindful acceptance) were associated with lower DMN activity than distraction. Specifically, focused attention was associated with lower activation in the precuneus, a DMN region associated with maintaining self-consciousness during self-referential processes.[54] Lower activity in the precuneus during focused attention is consistent with meta-analytic findings in adults.[40] Lower DMN activity in the focused attention condition may reflect a suppression of self-referential thoughts evoked by negative stimuli, and may therefore protect against depressive rumination in children. Relative to distraction, mindful acceptance was associated with lower activity in the MFC, which is consistent with a prior emotion regulation study in adults.[20] Other studies have reported reduced activation in the MFC during sustained meditation,[55] negative autobiographical memory recall, and acceptance of present emotional state.[56] Lower MFC activation observed during mindful acceptance may reflect reduced elaboration and appraisal of emotional experiences. Taken together, although distraction and meditation techniques are both known to be effective for reducing children's pain and distress, the present findings suggest that meditation techniques may be more effective for modulating DMN activity in children with cancer. Given that higher DMN activity is implicated in depressive rumination,[32,56] these findings imply a potential long-term protective role of meditation for helping children cope with stressful experiences.

Although we observed differences in the brain between conditions, there were no differences in distress ratings. We may have been underpowered to detect changes in distress ratings. Prior studies support beneficial effects of meditation on self-reported pain and emotional distress in children over time (e.g., over 4- or 8-week programs)[36] or following a single session.[25] We also observed minimal differences in brain activity between conditions, which should be examined in future studies with larger sample sizes. However, we found preliminary evidence that focused attention may be more effective for downregulating DMN activity than mindful acceptance, which may reflect the fact that paying attention to the breath may be a simpler, anchoring concept for children. This finding is interesting given results of a prior study in healthy adults showing that experienced meditators were better than beginners at downregulating MFC activity in response to emotional images.[21] Therefore, more experience with meditation may improve the ability to attenuate DMN activity. Further, although levels of trait mindfulness in our study were, on average, similar to those reported in prior studies in youth,[57,58] we did not observe associations between mindfulness levels and brain activity during the task in our exploratory analyses. Future studies with larger sample sizes should explore whether these effects are related to baseline mindfulness levels, or whether trait mindfulness predicts response to meditation-based interventions.

4.1 | Limitations

Our sample consisted of a relatively small sample size of children with cancer, and results may reflect the unique neurobiology of this population. Further, our sample consisted of both survivors and children undergoing active cancer treatments, which may confound any group comparisons. However, our hypotheses and analyses focused on a within-subjects approach. Sampling limitations are attributed to the low base rate of childhood cancer, which precluded our ability to examine sex differences in neural or behavioral measures. However, the sample size in the present study ($n = 12$) is consistent with previously published neuroimaging studies in pediatric cancer survivors (e.g., $n = 8, 15$),[59,60] and we used multiecho fMRI imaging techniques to further increase study power. We focused on children with cancer, because this pediatric population is exposed to disease- and treatment-related stress, is at increased risk of emotion dysregulation,[39] and because martial arts-based meditation programs have shown to be effective for reducing pain and emotional distress in this population.[24,25] In addition, the relatively wide age span (5–17 years) is a limitation due to differences in functional connectivity in young children compared to older teenagers. Another limitation is that we examined two forms of meditation (i.e., focused attention, mindful acceptance) and one non-meditation emotion regulation strategy (distraction), which may not be representative of all available emotion regulation techniques. In addition, we did not have a non-distressing (e.g., positively valenced) condition to compare our activation patterns to, so it is unclear if the resulting neural activation patterns are specific to regulation of negative stimuli. Additionally, all participants had at least 4 hours of meditation instruction. Findings may differ based on meditation experience,[21] as these techniques become more automatized. The brief meditation training may also influence neural activity during the non-meditative conditions, such as distraction. Therefore, future studies should examine different forms of meditation and the impact of meditation experience. Future studies should also integrate measures of both state and trait mindfulness.[15]

4.2 | Conclusions

Mounting evidence indicates that meditation is an effective approach for regulating pediatric pain and emotional distress. Mindfulness- and meditation-based interventions may be particularly well suited for children, because they do not engage CEN control systems, which are underdeveloped in youth, are easily accessible to children, and can be adapted to developmental age. Indeed, the present findings suggest that simple forms of meditation, such as focused attention to breath and mindful acceptance, can reduce activity in the DMN in children with relatively limited meditation training. Given alterations in the DMN are linked to various forms of psychopathology,[61] these results suggest that meditation emotion regulation techniques may be effective for modulating DMN activity in youth. These results also have implications for the management of pain and distress in pediatric healthcare settings (e.g., needle-related procedures), and for mitigating negative effects of stress and trauma in pediatric population that encounters disproportionally high stress (e.g., chronic health conditions).

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CONFLICT OF INTEREST

Elimelech Goldberg is founder and global director and Martin H. Bluth is the global medical/scientific director of Kids Kicking Cancer, a non-profit organization that developed the martial arts intervention. This work was supported, in part, by the St. Baldrick's Foundation and the National Institute of Mental Health to Hilary A. Marusak, and she had previously received grant funding from Kids Kicking Cancer. The authors declare no other conflicts of interest. Funders were not involved in the conduct of the study, data analysis or interpretation, or decision to publish.

ORCID

Jeffrey W. Taub https://orcid.org/0000-0003-2228-3235
Hilary A. Marusak https://orcid.org/0000-0002-0771-6795

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Treating pain in children can teach us about treating pain in adults

Instructor Sensei Giuseppe of Kids Kicking Cancer Italy, teaching a young cancer patient in Bergamo, Italy, on June 6, 2018. Elimelech Goldberg/Kids Kicking Cancer Italy , CC BY-SA

Author

Hilary A. Marusak
Postddoctoral research fellow,
Wayne State University

The U.S. government declared a national public health emergency in October 2017 to address the opioid addiction crisis. More than six months later, the country is still in the throes of the crisis, with no sight in end.

With the nation's spotlight on addiction to pain medications, the underlying epidemic of chronic or severe pain goes largely ignored. Further, although it's hard to know how people are treating their pain, survey data indicate that a third are on prescription pain medications. Indeed, more than 100 million U.S. adults are living with some form of chronic or severe pain. This is more than the number of people living with diabetes, heart disease or cancer, combined.

Almost half are not getting the pain relief needed from medications, and many pain medications have side effects ranging from constipation, nausea and vomiting to addiction and overdose. Many are seeking alternative approaches to pain management. Some surprising answers may come from a group of kids with cancer.

I'm a neuroscientist who studies the adverse effects of painful experiences in children, and we are finding that kids may be able to change the wiring of pain systems in the brain – without medications.

Two girls with cancer, displaying some of the side effects of cancer treatment such as hair loss, exhibit their resilience. Bill Branson/National Cancer Institute

The emotional toll of childhood cancer is so unbearable that it is sometimes easy to overlook that extreme physical pain that children with cancer undergo. The "cure" for childhood cancer includes invasive and sometimes painful treatment procedures, including venipunctures (blood draws), port-starts, spinal taps and bone marrow aspirations, which is a procedure that involves taking a sample with a syringe from the spongy tissue found inside bones. On top of that, chemotherapy can cause painful neuropathy, nausea and diarrhea, in addition to pain caused by the tumor itself.

Although pain is often under-recognized in children, those who treat this population see this pain every day and thus make treating children's pain a top priority. As a result, novel pain treatments sometimes first emerge to treat kids.

The perception of pain happens in the brain, in regions of the so-called pain matrix, including the anterior cingulate cortex, thalamus and insula. These brain regions are involved in a wide range of cognitive and emotion-related processes, and critically, seem to be involved with why pain feels so bad, or what is called the affective aspects of pain. Importantly, regions of the pain matrix continue to develop throughout childhood, making them especially sensitive to repeated pain exposures. So the frequent pain experienced with childhood cancer and cancer-related treatment procedures early in life may be especially harmful to the developing nervous system.

In some of the research studies conducted by our group and others, we have found that childhood cancer affects the functioning of the pain matrix. Changes in brain structure and function may contribute to chronic pain and other long-term or "late" effects commonly reported by childhood cancer patients and survivors, such as memory and attentional problems.

Given the potential for negative effects on the developing brain, the media attention about the opioid epidemic, and the fact that in some cases, children are already receiving thousands of pills over the course of their cancer treatment, physicians need alternative non-pharmacological approaches to pain management to address pediatric cancer pain.

New answers to pain?

One such promising approach is Kids Kicking Cancer, a nonprofit organization that is now in five different countries and using martial arts techniques to empower children beyond the pain, distress and uncertainty of their disease. The therapy of Kids Kicking Cancer involves a variety of mind-body interventions that are science-based, including mindfulness, meditation, breathing and visualization.

In a recent study, colleagues in my research group demonstrated that Kids Kicking Cancer is an effective intervention for reducing pediatric cancer pain, with nearly 90 percent of children reporting a reduction in pain by an average of 40 percent over the course of a one-hour session. Few if any pain medications of any kind have demonstrated such dramatic results.

Now, our lab at Wayne State University is using brain imaging to study how this works. Although the study is still underway, some of our preliminary results suggest that children with cancer are able to use these techniques to take control of their lives and rewire their brain's pain matrix.

These techniques may work by not getting rid of the pain signals coming in to the brain, but rather, by changing how distracting or 'salient' the brain sees them. In other words, these techniques may help to control pain by turning down its volume control - pain is just some of the many signals in the brain and people don't have to pay attention to it. And, importantly, these techniques appear to bypass the opioid receptors in the brain.

We adults may have a lot to learn from these children. One of the most unusual elements of Kids Kicking Cancer is that the children with cancer become the teachers. Indeed, the Kids Kicking Cancer "Heroes Circle" program allows for the children to show adults and other children how to "breathe in the light and blow out the darkness" of stress, anger and pain. Our research group hosted a Kids Kicking Cancer seminar with adults and found that almost 100 percent of participants – 97 percent, to be precise – reported that the seminar had a "profound impact" on their lives.

In this seminar, they learned from children battling cancer that the "Breath Brake" can be used to help them overcome challenging stress. By integrating these techniques into their own lives, they can lower their own stress and anxiety but also help to reduce pain and suffering of the children. Thus, these age-old mind-body techniques – combined with a platform that provides a purpose to look beyond themselves to others for inspiration - may be a powerful underutilized therapeutic tool to help adults suffering from pain, addiction or trauma.

In partnership with the state of Michigan and the Wayne State University methadone clinic, we are now testing whether the Kids Kicking Cancer Heroes Circle program can reduce pain among adults addicted to opioids and whether the brain systems underlying pain and addiction can be rewired. The therapy is simple, and involves breathing and guided imagery, such as using visualization to extract pain by "making holes" through the pain.

The first recommendation in the CDC's guidelines for doctors for treating chronic pain was to try non-pharmacological, non-opioid interventions first. So maybe we should look to some of our nation's young superheroes who are battling cancer for some answers to address the epidemic of pain and addiction.

Understanding the Psychological Effects of Childhood Cancer

By Hilary Marusak on July 24, 2018

Credit: Getty Images

Many forms of childhood cancers have gone from being a death sentence to a curable disease. Thanks to advances in treatments, the overall survival rate for childhood cancers has increased from 10% a few decades ago to nearly 90% today. This means that by the year 2020, an estimated half a million survivors of childhood cancer will be living in the U.S. With more children surviving, though, it has become increasingly clear that cancer and the subsequent treatments, such as chemo or radiation therapy, can have long-term negative effects that extend beyond physical problems such as hair loss, pain, and physical disability. Indeed, similar to "chemo brain" in adults, childhood cancer and its treatment may have harmful effects on brain development, causing problems with attention, memory, and language, and also leading to depression and anxiety. Based on studies using neuroimaging to examine brain structure and function also suggest that the treatments that are needed to save children's lives can also be harmful to neural development.

However, cancer and its treatment may not be the only damaging factors to consider. Childhood cancer is extremely stressful, for the patient and for the whole family. Stress begins at the time of diagnosis, when families are confronted by the tremendous burden of understanding the disease and medical terms, and facing the possibility of the child's death at a young age. Family life is disrupted as families struggle with a 'new normal' that consists of frequent hospital visits, overwhelming medical bills, and a questionable future. And then there are the stressful and sometimes painful medical procedures. Treatment for childhood cancers is often more intensive than for adult cancers, in part because the disease is more rapidly progressing than adult cancers, but also because children's bodies can tolerate more than adults can. This means that the side effects of treatment—nausea, fatigue, diarrhea, vomiting, and hair loss—can also be more severe.

The transition into survivorship brings its own set of challenges as families readjust to home and family life, and children re-enter school and social settings. Children may be years behind in school, and faced with the challenge of lasting attentional and memory problems, as well as hearing loss and other physical limitations. There is a constant fear of relapse which leaves families on guard—is that headache normal? We should not only consider the effects of cancer treatments on brain development but also the impact of childhood cancer as a stressful and potentially traumatic experience.

The long-term psychological effects of intensive cancer treatments in children have been a topic of study since the 1980's. As a group, childhood cancer patients cope psychologically well with the experience, but still, many report anxiety, depression, and even posttraumatic stress. Among children with cancer, research suggests that specific posttraumatic stress symptoms occur more frequently than the full spectrum of posttraumatic stress disorder (PTSD) and may affect nearly 75% of youth during or after treatment. There is substantial variability, with some studies suggesting that perceived life threat or clinically-related factors (e.g., length of hospital stays, reoccurrence, treatment intensity) are associated with more severe posttraumatic stress symptoms. Posttraumatic stress symptoms may include nightmares or flashbacks, a desire to avoid people, places, or things associated with the experience, a difficulty in feeling emotions, feeling helpless, distant, or cut off from others, and feeling anxious or easily startled. These symptoms may be experienced by children and their parents as well as siblings.

Although the psychological effects of cancer have been recognized for several decades, how the stressful and potentially traumatic aspects of childhood cancer affect brain development has been largely ignored. This is despite compelling evidence that stress and trauma experienced during childhood can significantly alter the developing nervous system. Changes in neural development may be lifelong, and increase risk for a range of physical and mental health problems throughout the lifespan. Indeed, in the landmark Adverse Childhood Experiences (ACES) study, published in the late 1990's, it was demonstrated that childhood trauma (e.g., violence, abuse, neglect) is extremely common, with more than 50% of adults reporting exposure to one or more forms. The study also identified childhood trauma as major risk factor for physical and mental health problems including cancer, heart disease, depression, and suicidality. These are major causes of death and disability around the globe.

Neuroscience research has shown that certain brain regions may be more susceptible to stress and trauma during childhood. Previous research by our group and others demonstrates that brain regions such as the hippocampus (involved in learning and memory), the amygdala (involved in emotion-related functioning) and the prefrontal cortex (involved in attention and other higher-order executive functions) are altered in individuals exposed to childhood trauma. Because these brain regions continue to develop across childhood, they may be particularly sensitive to insults such as stress, trauma, or chemotherapy. Therefore, we must consider the 'double hit' of cancer treatments and the stressful and potentially traumatic aspects of the experience on brain development.

We must recognize that childhood cancer is not only a physical disease but also a mental one. Helping families to cope with these stressful experiences should be a priority during treatment. However, strained for time and resources, psychological support from social workers, therapists, or Child Life advocates is sometimes inadequate in hospitals. These psychosocial support staff are not in every hospital, and may only see the families once during the course of treatment, if at all. Families have also reported that the support they receive drops off tremendously when the child completes treatment, leaving them with few resources to deal with the new stressors that adjusting back to normal life brings. In addition to pushing for cures for cancer, we should also advocate for psychological support as a standard of care for childhood cancer. This means having social workers, therapists, and Child Life advocates as a part of the treatment team, and with the family every step of the way.

We must push for new ways to prevent long-term damage. We need research to find evidence-based ways to build more healthy and resilient brains for children. For example, our research group at Wayne State University is currently performing neuroimaging studies to test whether a martial arts therapy, Kids Kicking Cancer, can reduce pain and promote healthy brain development. Because the brain is more plastic during development, it is not only more sensitive to cancer treatments and stress, but may also be more receptive to all the help we can provide.

How to access the healing power of children

Sep 28, 2020

By Martin H. Bluth, MD, PhD

Children have a unique power to integrate their realities in ways that we adults have long forgotten. It may be time for healthcare organizations to tap into that quality children possess to promote healing.

When I was a child, there was a prevalent view that "Children should be seen and not heard." Adults ruled, and children would be addressed when convenient. The notion was exemplified by George Banks, who was eventually influenced by the magical Marry Poppins to adopt a more enlightened view.

I recall my unenlightened pediatrician talking to my mother while I was being poked and prodded as if I was not a sentient entity. At one point, I yelled at him, "Hey, talk to *me*! I'm not a piece of meat."

Too often, children are treated as less than fully developed human beings who are needy and inclined to make exasperating demands on us. We love them, but they also test our patience, and we assume they must grow and evolve before they can offer any meaningful contributions in the adult world.

But perhaps that view is short-sighted.

Many have attested to the power of children to promote healing, and we should not be too quick to dismiss such reports as being fanciful.[a] Children have a unique perspective of the world that can provide a lesson for adults on maintaining and improving mental and physical health. And their ability to openly convey that perspective goes far beyond the warm and fuzzy feeling one derives when marveling about a sleeping infant.

Just to be clear, I am not suggesting that children be used as crutches to help their parents deal with psychological and emotional traumas, which unfortunately does occur.[b] Rather, I am suggesting that we should appreciate children's unique power to integrate their realities in ways that adults have long forgotten.

Children's propensity for mindfulness

As an example, the ability of children to transcend their disease states in unique ways has begun to catch the attention of the healthcare community. Children have a heightened ability to use mindfulness-related approaches to decrease anxiety and stress. The have a capacity for being present-minded through a natural ability to focus on noting, observing and accepting the present moment, without judgment.[c]

Researchers have found that cognitive control, flexibility and memory in children with ADHD improved with mindfulness-based meditation and that these improvements were considerably more robust in children than adults.[d] I have also seen clear evidence that martial-arts-based meditative intervention can help children with cancer and other disease states manage their illness in a non-conventional manner, incorporating elements of mindfulness, psychosocial temperance in addition to tai chi and other elements.

This method does not simply attempt to distract children from thinking about their condition. It actually imbues the child with a sense of power, peace and purpose, thereby changing their perception and receptivity to their environment, emotions, interactions and disease-related insults and impositions.[e]

The benefits of cultivating mindfulness in children – and adults

The power comes from the way activities focused on promoting mindfulness can move a patient from a state of passive acceptance of their predicament to becoming actively engaged in each life experience. The patient acquires a gestalt of peace, where disease-related melancholia and corresponding negative stagnation rather give way to an empowering sense of purpose. This transformation instills in patients a conviction that helps them transcend their disease-state. It also conveys that idea to others, demonstrating how one can not only cope with a disease but also ameliorate it. This approach is now practiced globally, and it has be recognized by CNN and others as a paradigm shift in healthcare management.[e]

Further, disease can affect not only the patient but also all family members, fostering disruptions caused by the need to allocate resources and attend to the sick child, in addition to the impact on the siblings and other life metrics.[f] The mindful approach can counter these effects by unifying, rather than splintering, the family around the patient's care. As a martial artist and tai chi-ist for more than 20 years, I recall my sensei saying, "The family that kicks together, sticks together." And my experience has shown that is often the result.

Economic viability

The practical question for cash-strapped health systems is, "What about the cost, and even if it's affordable, how could we begin to invest in promoting such programs?" The good news is that the economics of a such an approach appear to be favorable to the healthcare system. Most of these programs are incorporated into the healthcare and hospital setting as volunteer programs, often supported through philanthropy and grant funding, and they are designed to work synergistically with conventional healthcare to augment patient improvement.

Furthermore, in the current epoch of COVID-19, such interventions can occur in the virtual setting, as a means to reach socially distanced, homebound and isolated individuals. Online options can include both individual "one-on-one" interactions as well as access for patient and their family to a virtual community as an adjunct to allopathic therapy and management.

The cost centers are modest, and the idea of introducing such initiatives as a *standard of care* has been promoted as a value-added offering in healthcare training curricula and as a general cost containment benefit to the general healthcare system.[g] Moreover, billing for services can be instituted under select CPT codes for revenue cycle management.[h]

Engaging children to promote healthcare improvement among adults

The positive effect of children on adults' state of health is novel. Other countries have begun assessing the potential benefits for select healthcare settings. Israel has begun a pilot physical therapy program for adult seniors that integrates a connection with children. Another pilot program incorporated the mindfulness approach drawn from the martial arts therapy practiced by children with cancer to positively affect adult patients with substance use disorder by significantly reducing their pain, drug craving anxiety and depression over a 12-week study period.[i]

4 ways to move forward

To tap into the potential benefits of such an approach, finance leaders of hospitals and health systems can begin with four practical steps.

1. Assess the clinical landscape. Finance leaders should identify the service lines and disease spaces in their organizations' healthcare milieu that offer the potential for active engagement. For example, a pediatric cancer hospital should be able to employ already existing resources, while a pediatric obesity clinic would need to institute only a few minor adaptations toward implementing such a method.

2. Determine output measures of success. This recommendation applies to any service, and to patients of any age range. Tai chi programs have been shown to decrease pain and increase range of motion in those suffering from arthritis, for example.[j] Pain scores have been shown to decrease in children with cancer upon implementation of a martial-arts-based meditative intervention. Measures of success can range from a simple questionnaire to changes in biometric parameters, pain scales and laboratory values.

3. Interact with the organization's constituencies. The communities served by a healthcare domain can be very supportive of such initiatives. Promoting such avenues where children become the center focus to help themselves and others usually resonate with most community members, both healthy and sick, as a higher calling, ensuring such a program is well received.

4. Follow the numbers. Value can take the form of basic cost containment to patient and community allegiance. Monitoring such intangible metrics can provide value added outcomes for patient satisfaction and recruitment, attrition reduction, and hospital or clinic branding. Such value, in addition to conventional costs and receivables, can be monetarily defined and added, in many cases, to a balance sheet, as well.[k]

A new horizon for healthcare

In short, the healing power of children on each other as well as adults is curious and provocative. This novel approach can be incorporated into the healthcare system to maximize resources, empower patients, parents and family, improve revenue cycle management and provide evidence to the world that children can heal us and themselves in ways have not yet begun to imagine.

Footnotes

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Phonic.ai

Researcher Spotlight: Kids Kicking Cancer

Researcher Spotlight February 12, 2021 By Ashley Avarino

In this blog post, the spotlight is on Kids Kicking Cancer. We had the pleasure of chatting with Amanda Bluth, KKC's Research and Grants Coordinator, to learn all about how KKC's research is impacting children all around the world.

Phonic: What is Kids Kicking Cancer?

Amanda: Kids Kicking Cancer is a 501(c)(3) non-profit organization providing a unique, martial arts-based approach to palliative care for children suffering from cancer, sickle cell, heart disease, and other chronic illnesses.

Our work is concentrated around three areas:

1. Pain and stress management for very sick children
2. Creating resilience and support for otherwise healthy children
3. Inspiring healing and well-being in adults (ex: ARI)

Our non-contact, evidence-based techniques are delivered in person and virtually throughout hospitals, medical facilities, outpatient centers, home visits and schools across the United States and globally. Our goal with your help is to aggressively grow this program to affect one million children.

Phonic: When and why was Kids Kicking Cancer founded?

Amanda: Kids Kicking Cancer was created in 1999 by Rabbi Elimelech Goldberg (aka Rabbi G.), a black belt Rabbi and clinical assistant professor of pediatrics. Rabbi G. lost his first child to leukemia at the age of two and brings a wealth of personal experience and sensitivity to dealing with children and families facing life-threatening illness.

The organization has since evolved to become the Heroes Circle, an evidence-based global healing and wellness initiative inspired by the children of Kids Kicking Cancer.

Phonic: What's a typical program like at Kids Kicking Cancer?

Amanda: Without trying to sound too cliché, I would say Kids Kicking Cancer doesn't have a "typical" program. We have programs that deal with different populations that have different needs, but the core of our programming lies in creating something that will lower the pain of others through self-regulation and empowerment.

Phonic: What type of research do you do at Kids Kicking Cancer?

Amanda: Most of our research centers around evaluating whether our novel martial arts-based programs are effective for reducing pain and stress. We have several programs, including our founding program for children with cancer, but we have recently expanded to include other groups under our Heroes Circle umbrella, including children with sickle cell or other chronic illnesses, school children, and adults with substance use disorders.
Our research incorporates a variety of tools, including surveys and questionnaires, qualitative interviews, biological (e.g., stress hormone levels), and psychophysiological measures (e.g., EEG/ERP, SCR, MRI/fMRI, HRV). Some of these findings have already been published in quality peer-reviewed scientific journals. Check them out here, here, and here.

Phonic: How do you partner with academia to accomplish these goals?

Amanda: We partner with researchers at Wayne State University (WSU) and other institutions to meet our research objectives. For example, our Global Medical Director, Dr. Martin Bluth, is a professor of pathology at WSU School of Medicine (Detroit, Michigan) and Chief of Transfusion Medicine at Maimonides Medical Center (Brooklyn, NY). Dr. Hilary Marusak has also directed several of our studies in children and adolescents. She is a neuroscientist and assistant professor of psychiatry in the WSU School of Medicine. Dr. Mark Greenwald is an expert in the neuroscience of substance use disorders and led our research study in patients with opioid use disorder.

Phonic: Why did you choose to use Phonic in your research?

Amanda: Jessie Davis, a member of our Innovation team, discovered Phonic while looking for a school program survey tool that allowed respondents to record their responses instead of typing. When Jessie saw Phonic's recording feature, she was so impressed she presented it to the Kids Kicking Cancer team. At this point our Adolescent Young Adult (AYA) program team was also looking for a survey tool to use and was equally impressed by Phonic's abilities. This led to both programs deciding to use Phonic.

Phonic's use of text, audio, and video mediums allows us to have in-depth insight into how our programs are being utilized. We were particularly impressed with the ability to use recordings, which Phonic transcribes and can be used
to classify affect and emotion. Phonic is also being used to determine program barriers which help inform us how to pivot as we develop and scale our programs. These innovative tools truly set it apart from other candidates, as it allows for the collection of more robust data.

Phonic: How do you use Phonic in your research?

Amanda: Phonic is currently being used for our AYA program and our Heroes Circle in-school curriculum. Our AYA program targets teens and young adults that want more targeted programming for their journey into adulthood (life skills, mentoring, self-esteem, etc.). We have created several types of Phonic surveys to measure program satisfaction, changes in physical, psychological/emotional, academic, and social functioning throughout the program, and Kids Kicking Cancer's relevance in participants' lives.

In partnership with Oak Park Michigan School District, our Heroes Circle in-school curriculum focuses on teaching students the techniques to help them self-regulate as they encounter a range of stressors. At the same time, they increase personal empathy as they are encouraged to use their techniques to teach their family, friends and community. The program has an extensive curriculum that was built to address the effects of stressful situations, thereby improving a child's ability to self-regulate and learn. Using a "surround-sound" approach, this program is integrated into the classroom and extended to teachers, psychosocial staff, and other high-touchpoint staff. We use Phonic for our "Breath Brake Coach" (psychosocial staff with advanced training in the school program curriculum) surveys, consisting of a monthly survey and end of year evaluation; additionally, Phonic was used for school program surveys for non-Breath Brake psychosocial staff.

Phonic: What's the best part of working with kids through Kids Kicking Cancer?

Amanda: I get so inspired by the kids in our programs! At Kids Kicking Cancer, we teach our kids that they are powerful martial artists and can teach the world. I truly feel their power and wisdom! As kids go through our programming, they are able to transform from a state of fear and pain to one of control, determination, and empowerment. I think there is a lot we can learn from each and every one of them – whether it's kindness, friendship, courage, or confidence. Our kids are self-regulated, aware, and motivated to do good in the world and that is why they have the power to teach the world.

It’s all in the breath: An argument for improved outcomes and reduced costs in healthcare

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By Martin H. Bluth, MD, PhD

Effective breathing may not be on many healthcare finance leaders’ radar as an important area of focus for healthcare providers. But *ineffective* **breathing can be a prelude to more severe health problems.**

I have noticed that I have been experiencing occasional difficulty breathing recently. It seems to occur whenever I am near someone who coughs or who tells me they have interacted with someone who tested positive for COVID-19. Sure, it also occurs after I have sprinted up a flight of stairs to my with my 15-pound backpack while wearing a mask — that's to be expected. But in the first two instances, catching one's breath is an only natural subconscious response to the gravity of COVID-19.

My prescription in such cases remains the same: Perform deep breathing and chi gong, and of course, listen to the first few bars of Rush's *Tom Sawyer* turned up to *11*. (If you've seen "Spinal Tap," you'll know what I mean.) These things all help me expand my lungs, clear my head and find some peace amid the chaos.

A fundamental contributor to good health

Breathing is essential. We all know this. However, what many may not appreciate is that introducing a modicum of active control over our breath can have remarkable therapeutic advantages.

There's one type of breathing that we all have seen: the expanded chest, military-like version seen in soldiers standing at attention. However, there is another approach to breathing that is more conducive to good health: It is the abdominal/diaphragmatic breathing that starts with the expansion from the lower waist up. Think newborn-baby breathing.

Both approaches are effective. But abdominal/diaphragmatic breathing can provide a greater tidal volume (normal volume of air displaced between normal inhalation and exhalation) and total lung capacity (maximum volume of air the lungs can accommodate after maximum inspiration). It therefore provides more breath and oxygen to sustain the body.

Some expand this idea further, suggesting good breathing comes in through the nose and out through the mouth, creating a conscious cycle. This approach is sometimes enhanced with imagery (e.g., breathing in light with inhalation, breathing out darkness with exhalation) to further potentiate and maintain the remarkable therapeutic effect of the breath.[a]

But it doesn't stop there. Initiating slow purposeful breathing also provides a momentary mindfulness of one's state of being, to calm the mind.[b] Moreover, controlling one's exhale has also been shown to engage and facilitate activity of the vagus nerve (described by some as the body's *master switch*) in ways that improve relaxation and promote mental and physical health.[c] A controlled exhale can engage the diaphragmatic muscles, further amplifying these anxiolytic responses providing a non-addictive calming effect without the need for prescription drugs. The more you remain active, engaged and conscious of your breathing, the better you feel and the better you are.

A place in healthcare for a focus on breathing?

Can we institute breathing modalities in our overworked, overbudget healthcare industry? Would it be cost effective?

You may be surprised to learn that the answer to both questions is "yes."

Breathing therapy has been implemented in some healthcare domains around the U.S. and has shown improved outcomes and function in select disease states.[d] Furthermore, recent reports have also demonstrated improved outcomes in physiologic/quality-of-life parameters (e.g., asthma) and their reduction in related healthcare costs, which can translate into cost saving through decreased hospital visits and related morbidities.[e]

Using this concept, healthcare leaders can introduce the following approaches in their healthcare settings:

1. **Take a breathing break**, and encourage employees, staff, faculty and others in the organization to employ breathing exercises to rejuvenate themselves. (Tutorials can be accessed via web-based apps, videos and tailored instruction.)
2. **Teach the relevance of focused breathing exercises** to medical students, residents, fellows and faculty to incorporate in their daily activities and impart to their patients, thereby initiating a culture of well-being at a low cost.
3. **Provide portals on breathing exercises to patients** to improve retention and visibility of patients under a less medical gestalt, thereby also fostering their greater receptivity.

It also can be useful to conduct brief satisfaction or other functional surveys to track the progress and value of the initiatives and to gauge how the targeted groups are responding to the focused intentional breathing and the extent that they report an improved sense of well-being.

We often take breathing for granted. But consider: Is there any other activity *accessible to our voluntary control* that we must sustain every moment in order to continue living? By recognizing the subtleties of breath and its intrinsic role in keeping us alive, we raise our consciousness about the health benefits of one of life's simplest activities, and we can improve it with minimal effort. So embrace the principles of effective breathing. Your mind and body will thank you for it.

Footnotes

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POWER PEACE PURPOSE

KIDS KICKING CANCER

27600 Northwestern Hwy., Suite 220
Southfield, MI 48034

248.864.8238

HeroesCircle.org