Brain Imaging and Behavior (2016) 10:258–271
DOI 10.1007/s11682-015-9390-8

ORIGINAL RESEARCH

Functional MRI in medulloblastoma survivors supports prophylactic reading intervention during tumor treatment

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Abstract Development of reading skills is vulnerable to disruption in children treated for brain tumors. Interventions, remedial and prophylactic, are needed to mitigate reading and other learning difficulties faced by survivors. A functional magnetic resonance imaging (fMRI) study was conducted to investigate long-term effects of a prophylactic reading intervention administered during radiation therapy in children treated for medulloblastoma. The fMRI study included 19 reading-intervention (age 11.7±0.6 years) and 21 standard-of-care (age 12.1±0.6 years) medulloblastoma survivors, and 21 typically developing children (age 12.3±0.6 years). The survivors were 2.5 [1.2, 5.4] years after completion of tumor therapies and reading-intervention survivors were 2.9 [1.6, 5.9] years after intervention. Five fMRI tasks (Rapid Automatized Naming, Continuous Performance Test using faces and letters, orthographic and phonological processing of letter pairs, implicit word reading, and story reading) were used to probe reading-related neural activation. Woodcock-Johnson Reading Fluency, Word Attack, and Sound Awareness subtests were used to evaluate reading abilities. At the time of fMRI, Sound Awareness scores were significantly higher in the reading-intervention group than in the standard-of-care group ($p=0.046$). Brain activation during the fMRI tasks was detected in left inferior frontal, temporal, ventral occipitotemporal, and subcortical regions, and differed among the groups ($p<0.05$, FWE). The pattern of group activation differences, across brain areas and tasks, was a normative trend in the reading-intervention group. Standardized reading scores and patterns of brain activation provide evidence of long-term effects of prophylactic reading intervention in children treated for medulloblastoma.

Keywords Functional magnetic resonance imaging · Reading intervention · Children · Brain tumor · Cancer survivors

Background

Medulloblastoma is the most common malignant brain tumor in children, and innovations in treatment have yielded steadily increasing survival rates in recent decades. With current multimodality treatment protocols, which comprise maximal safe surgical tumor resection, tumor bed and risk-adapted craniospinal irradiation, and adjuvant chemotherapy, the medulloblastoma survival rates exceed 80 % for children with standard-risk disease and 60 % for those with high-risk disease (Gajjar et al. 2013). Patients with the medulloblastoma subtype of genetic mutation in the WNT molecular signaling pathway (Gibson et al. 2010) are effectively 100 % curable. With more patients surviving this once deadly disease, the quality of life for medulloblastoma survivors is a pressing concern.

Electronic supplementary material The online version of this article (doi:10.1007/s11682-015-9390-8) contains supplementary material, which is available to authorized users.

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Late cognitive deficits in long-term survivors of brain tumors are well documented and may progressively worsen over the years (Butler and Haser 2006; Dennis, Spiegler, Hetherington, and Greenberg 1996; Glauser and Packer 1991; Maddrey et al. 2005; Mulhern et al. 1998, 1999). These deficits can be sufficiently severe to hinder normal academic achievement, vocational attainment, and quality of life. Deficits have been reported in many cognitive domains, including attention, processing speed, working memory, executive functions, intelligence, and academic skills. Reading may be particularly vulnerable to disruption in brain tumor survivors (Mulhern et al. 2005; Schreiber et al. 2014; Conklin, Li, Xiong, Ogg, and Merchant 2008), and impaired reading may underlie other learning difficulties and have a leading role in IQ loss (Ramsden et al. 2013) and academic failure in medulloblastoma survivors.

Mitigating adverse effects of treatment on brain function while sustaining or improving survival is the core objective for innovations in medulloblastoma therapy (Gajjar et al. 2013). Tumor treatments, especially cranial radiation therapy, often cause detrimental late cognitive effects (Mulhern et al. 1998, 2005; Gajjar et al. 2013; Merchant, Happersett, Finlay, and Leibel 1999; Rodgers, Trevino, Zawaski, Gaber, and Leasure 2013); conformal radiation therapy and risk-adjusted radiation dose have been used to minimize neural toxicity and long term cognitive sequelae in survivors (Merchant et al. 1999).

Along with efforts to reduce the neural toxicity of tumor treatment, cognitive intervention programs have been conducted in the growing population of survivors. Pharmacological intervention with methylphenidate was evaluated for addressing attention deficits in childhood cancer survivors (Conklin et al. 2009, 2010a, b; Mulhern et al. 2004). There was measurable benefit for some patients, but stimulant medication was contraindicated in some cases and there was parental concern of possible drug side effects (Conklin et al. 2010a, b). Therapist-delivered cognitive remediation in survivors was typically more welcome by parents and improved some behavioral measures, but the long-term effect and generalized improvement in academic skills remain uncertain (Butler et al. 2008). Cognitive remediation is also time-consuming and expensive, with limited availability for patients living far from major medical centers. Recently, computer-based training programs for cognitive remediation in childhood cancer survivors were shown to be feasible and may improve working memory (Hardy, Willard, Allen, and Bonner 2013).

In addition to remedial cognitive interventions, prophylactic interventions during tumor therapy may be feasible and potentially beneficial. We recently conducted a trial of prophylactic reading intervention administered during the radiation therapy phase (Palmer et al. 2014) in a medulloblastoma clinical protocol, SJMB03 (NCT00085202, clinicaltrails.gov). The reading intervention was well accepted by families; but at the time when the radiation therapy and reading intervention were just completed, no significant differences were found in decoding scores between the reading-intervention participants and the standard-of-care patients (Palmer et al. 2014).

To further characterize the outcomes of this prophylactic intervention trial, we conducted a post hoc functional magnetic resonance imaging (fMRI) study of neural systems for reading in a subset of the medulloblastoma survivors who had participated in the reading intervention trial and were at least 1 year since completing tumor therapy. FMRI in pediatric brain tumor survivors is feasible (Zou et al. 2005; Wolfe et al. 2013), and is helpful in understanding and evaluating effects of cognitive remediation programs conducted with these survivors (Zou et al. 2012). FMRI has been used widely in studies of language and reading in healthy adults and typically developing children and provided much understanding of the brain system for reading and its development in the past 20 years (Price 2012; Pugh et al. 2013; Turkeltaub, Gareau, Flowers, Zeffiro, and Eden 2003). In children with dyslexia or other reading impairment, fMRI revealed different patterns of brain activation for reading tasks (Gebauer et al. 2012; Temple et al. 2001; Raschle et al. 2012). In fMRI studies of reading interventions, changes of activation in brain regions or networks supporting reading process were observed after intervention (Gebauer et al. 2012; Simos et al. 2002; Shaywitz et al. 2004; Temple et al. 2003). Brain activation involved in reading often includes left hemisphere temporoparietal, occipitotemporal, and inferior frontal regions, as well as other visual and subcortical sites (Price 2012, 2013; Pugh et al. 2013). Left ventral occipitotemporal (vOT) region or left middle fusiform area has an established role in reading process (Cohen et al. 2003; Kherif, Josse, and Price 2011; Price and Devlin 2011; Seghier and Price 2011; Turkeltaub, Flowers, Lyon, and Eden 2008). The Left vOT includes an area dubbed the visual word form area because of its responses to written words compared to other objects. Because of its proximity to the tumor site and radiation treatment volume, we hypothesized that brain activation during reading tasks in the vOT area would be diminished and the abnormal vOT activation may account for early visual letter or word recognition difficulties that lead to later reading deficits in medulloblastoma survivors. We also hypothesized that prophylactic reading intervention during radiation therapy might mitigate the loss of reading skills and fMRI may provide neural evidence for the effects of the reading intervention.

Methods

Participants The fMRI study was approved by the St. Jude Children's Research Hospital IRB. Informed assent from each participant and written informed consent from the guardian was obtained. The follow-up fMRI study included 42

SJMB03 survivors from the original 81 patients in the prophylactic reading intervention study (Palmer et al. 2014), with 21from the 43 reading-intervention (INT) patients and 21 from the 38 standard-of-care (SOC) patients. Attrition factors included, unwilling to participate in fMRI, non-compliant with the fMRI study protocol, unable to complete the tasks, and disease progressions. The demographic and clinical characteristics of the subset of survivors in the fMRI study were similar to those of original population in the reading intervention trial (Palmer et al. 2014), and there were no significant differences between the INT and SOC groups (Table 1). In addition, 21 age- and gender-matched typically developing (TD) children were included in this fMRI evaluation (Table 1). The 21 TD children were randomly selected from 102 participants (age 6 to 25 years) recruited from local community for a large scale fMRI study of reading. All TD children were native speakers of English with no history of central neural system injury or disease, no history of attention deficits or learning disability, no major physical, neurological, or psychiatric condition, having not been treated with psychostimulants or psychotropic medications within 2 weeks before MRI or neuropsychological testing, and not wearing orthodontic appliances.

Both INT and SOC patients received standard academic instruction through the hospital's school program during their tumor treatment. In addition, the INT patients participated in the reading intervention (Fast ForWord, Scientific Learning Corporation) during the time period of radiation therapy, which was after tumor surgery and before chemotherapy. Details of the reading intervention have been published recently (Palmer et al. 2014) . The Fast ForWord program is a computer-based reading intervention designed to increase processing efficiency and improve reading skills (e.g., sound-letter associations, phonological awareness, and word recognition) via a game-like format that incorporates modified speech (Loeb, Gillam, Hoffman, Brandel, and Marquis 2009). For these 21 INT survivors, the average training time was 43± 2 min/session and the average number of sessions was 31±2. Data from 2 survivors in the INT group were excluded from analysis because they completed too few reading intervention sessions (0 and 3 sessions, Grubb's test U=0.38, p=0.005). There were no significant differences detected between the INT and SOC survivors for disease risk factors and ages at radiation therapy.

The study protocol included three fMRI and reading evaluations at 1 year intervals. At the time of the first fMRI, medulloblastoma survivors were 2.5 [1.2, 5.4] (median [min, max]) years after completing tumor treatment with 2.8 [1.2, 5.4] years for the INT and 2.5 [1.2, 4.5] years for the SOC. The INT survivors were 2.9 [1.6, 5.9] years after completing the reading intervention. The age was 11.7±0.6 years for INT survivors, 12.1±0.6 years for SOC survivors, and 12.3± 0.6 years for TD children (Table 1).

Reading Scores Reading abilities were evaluated with the Woodcock-Johnson III battery (Woodcock, McGrew, and Mather 2001) and our analysis included the Sound Awareness, Word Attack, and Reading Fluency scores at the time of fMRI for all participants . In addition, reading scores during the tumor treatment and before reading intervention for the survivors were retrieved from previous study (Palmer et al. 2014). Sound Awareness requires rhyming, deletion, substitutions and reversing of spoken sounds and is considered a measure of phonemic awareness. Word Attack requires

Table 1 Demographic and clinical characteristics of participants

	INT	SOC	p[1]	TD
N (Female:Male)	19 (7:12)	21 (6:15)	0.74	21 (7:14)
Age at 1st fMRI (years±stderr)	11.7±0.6	12.1±0.6	0.52	12.3±0.6
Race (Asian/Black/White/Other)	0/1/16/2	0/3/17/1	0.70	0/3/18/0
Age at Diagnosis (years±stderr)	10±0.6	9.5±0.6	0.54	n/a
Disease Risk Stratum (Average:High)[2]	16:3	13:8	0.16	n/a
Years after Tumor Treatment (Median [min, max])	2.8 [1.2, 5.4]	2.5 [1.2, 4.5]	0.80	n/a
Parent Age (years±stderr)	43.4±1.0	41.2±1.6	0.72	40.8±1.2
Parent Education (years±stderr)	15.6±0.5	14.0±0.5	0.09	15.9±0.3
Parent Marital Status (M/Sp/D/Sg/U)[3]	13/1/1/1/3	12/1/5/1/2	0.42	19/0/0/0/2

[1] p values for comparison between the INT and SOC groups. Fisher exact test for categorical variables, Wilcoxan test for continuous variables, for Years after Turmor Treatment, GEE model was used to account for the repeated measures

[2] All patients were treated radiation therapy and chemotherapy after maximal tumor resection. Average-risk patients were treated with 23.4 Gy and High-risk patients with 36–39.6 Gy cranio-spinal radiation, and both groups had 55.8–59.4 Gy 3D conformal boost to the tumor site. Patients in both groups were treated with four cycles of high-dose chemotherapy (cyclophosphamide, cisplatin, vincristine) after radiation therapy

[3] M/Sp/D/Sg/U corresponding to Married/Separated/Divorced/Single/Unknown for parent marital status

INT: reading intervention medulloblastoma survivors; SOC: standard-of-care medulloblastoma survivors; TD: typically developing children pronunciation of unfamiliar non-words and is considered a measure of phoneme to grapheme awareness. Reading Fluency requires timed reading of simple sentences and verification of veracity by circling yes or no. It is a higher order task of reading efficiency and comprehension. All scores are age standardized using a large, representative normative sample, resulting in scores with a mean of 100 and standard deviation of 15.

FMRI A Siemens Trio 3 T scanner was used for fMRI data acquisition with the following parameters: Single shot T2* weighted EPI, TR=2 s, TE=30 ms, FOV =192 mm, matrix =64×64, bandwidth=2055 Hz/pixel. The whole brain was covered by 32 slices with slice thickness= 3.5 mm.

Five fMRI tasks were used in the study and are summarized below. All stimuli were presented visually on a rear mounted screen and viewed via a mirror mounted on the head coil. Presentation® software (https://www.neurobs.com/) was used for stimulus delivery and logging the stimulus and response timing. The NULL condition, if included in a task, was to look at a small fixation cross at the center of the dark grey screen.

(1) Rapid Automatized Naming (RAN) was based on a standardized test often used to evaluate cognitive processes for fluent reading (Norton and Wolf 2012). The participant was presented with *Color* squares, *Numbers*, *Letters,* or a fixation cross and was to silently and rapidly name each color, number, or letter line by line during the task. Depending on the task condition, a screen with five lines of 10 color squares, numbers, or letters was shown for 20 s and the participant pressed a button after naming each line. Stimulus blocks were repeated 3 times each in the pattern of NULL—*Color—Number—Letter* and 135 image volumes were acquired for the RAN task (Misra, Katzir, Wolf, and Poldrack 2004).

(2) A Continuous Performance Task (CPT) was included to evaluate letter or object recognition, attention, and motor control functions (Ogg et al. 2008) as bases for the reading process. This was an event-related version of the CPT paradigm in which *Letter*, *Face*, or fixation cross (NULL condition) was presented centrally in a pseudo-randomized order. The task was to press a button for each target letter ("X") or target face (picture of a famous/family person). Stimulus presentation sequences were designed with the "permuted 2-block" strategy (Liu 2004) to achieve a nearly optimal efficiency and power to detect task-induced BOLD signal changes. Stimuli were presented for 250 ms with 1-s inter-stimulus interval and 125 image volumes were acquired for the CPT task.

(3) An Implicit Reading (IMPLICIT READ) task from a study of reading skill acquisition in healthy subjects (Turkeltaub et al. 2003) was included. Alternating blocks of 5-letter real words and 5-character false-font strings were presented, and the participant was instructed to press a button if the word or false-font string contained an ascender, letter or false-font character rising above x-height, such as b, d, f, h, etc. Half of the stimuli contained ascenders. Blocks of the *Word* and *False Font* were alternated with blocks of NULL conditions. Stimuli were presented for 1.2 s, with a 3-s inter-stimulus interval and 138 image volumes were acquired for the task.

(4) An Orthographic and Phonological processing of letters (ORTHOPHONO) task was adopted from studies of dyslexic children (Temple et al. 2003). Ten letters (BCDFGYWTVZ) and three short lines (|, \, /) were used as task stimuli. Pairs of letters or short lines were presented on the screen with 3 task conditions (*Rhyme, Same Letter, and Same Line*). During the *Rhyme* condition, the participant saw pairs of letters and was instructed to push a button if the names of the 2 letters rhyme. During the *Same Letter* condition, the participant saw 2 letters and was instructed to push a button if the 2 letters are the same letter of the alphabet. During the Same Line condition, the participant saw pairs of lines and was to push the button if 2 lines had the same orientation. The ORTHOPHONO task did not include a NULL condition. Stimulus pairs were presented for 3 s with 3.3-s inter-stimulus intervals in a 20-s block, with an instruction appeared on the screen for 2 s at the beginning of each task condition. Stimulus blocks were repeated 5 times each in the pattern *Rhyme—Same Letter—Same Line* and 155 images volumes were acquired for the task,

(5) Story reading (STORY READ) was an fMRI task used to evaluate language lateralization in pediatric epilepsy patients (Ries et al. 2004). Participants silently read a meaningful short story during the *Story* condition, and scanned "sentences" made of false font strings that had the length of typical words during the *False Font* condition. The STORY READ task had no NULL condition. The *Story* condition was presented on 4 consecutive screens in 24 s and the *False Font* condition was presented on 3 consecutive screens in 18 s. A total of 5 *Story* blocks interleaved with 3 *False Font* blocks and 144 image volumes were acquired for the task.

Image data analysis SPM (http://www.fil.ion.ucl.ac.uk/spm/) software was used in functional image processing and identifying group brain activation. Preprocessing of the fMRI images included realignment, normalization, and spatial smoothing. SPM5 was used in image preprocess and voxel-wise 1st level statistical analysis to identify activation maps for each individual. Contrasts of interest for each fMRI task were set and corresponding contrast images were generated for the 2nd level voxel-wise group analysis. SPM8 was used in the group analysis. A full factorial design was set up for the 3 groups (INT, SOC, and TD) for each fMRI session. Group effects, task effects, and group-by-task interactions were tested.

In addition, activation from three areas reported to support reading (Price 2012; Pugh et al. 2013) were used to explore relations between brain activation and behavior measures. Regions of interest (ROI) were defined as a 5 mm-radius spheres centered at the following MNI coordinates: (±43, −54, −12) in the left and right ventral occipito-temporal area (vOT), (±60, −34, 0) in left and right superior temporal sulcus and middle temporal gyrus (STS/MTG), and (±50, 11, 21) in left and right inferior frontal gyrus (IFG). The ROI locations are shown on the TD activation map for each of the fMRI tasks (Figs. 1, 2, 3, 4 and 5). The activation index in each ROI for each fMRI task was calculated as the mean t-value of the ROI.

Statistical analysis Statistical analyses were performed using SAS software 9.3. Generalized estimating equation (GEE) models (Liang and Zeger 1986) were used for inference with multiple measurements from each participant. Reading scores and activation index for each ROI were analyzed to detect time, group, and interaction effects (Reading Scores=Time+Group+Time*Group, or Activation Index=Time+Group+Time*Group). Correlation between the ROI activation index and the reading scores was evaluated while adjusting for group effects, and group-reading score interactions (Activation Index=Reading Scores+Group+Reading Scores*Group). In addition, survivors were grouped into 3 categories (Time Windows) based on the time since completion of tumor treatment. Reading scores were analyzed at each Time Window using Wilcoxon rank sum tests.

Results

All TD children completed the 3 protocol-based fMRI and reading evaluations, but INT and SOC survivors had missing evaluations. The number of evaluations included in each Time Window is reported in Table 2.

Reading scores The age standardized Woodcock-Johnson scores in Reading Fluency, Word Attack, and Sound Awareness and group comparisons of the scores are summarized in Tables 3 and 4. Before reading intervention (Time Window 0), the median Sound Awareness was higher in the INT group than in the SOC group, but the difference was not significant. There were no statistically significant differences between the two groups for any of the reading scores at Time

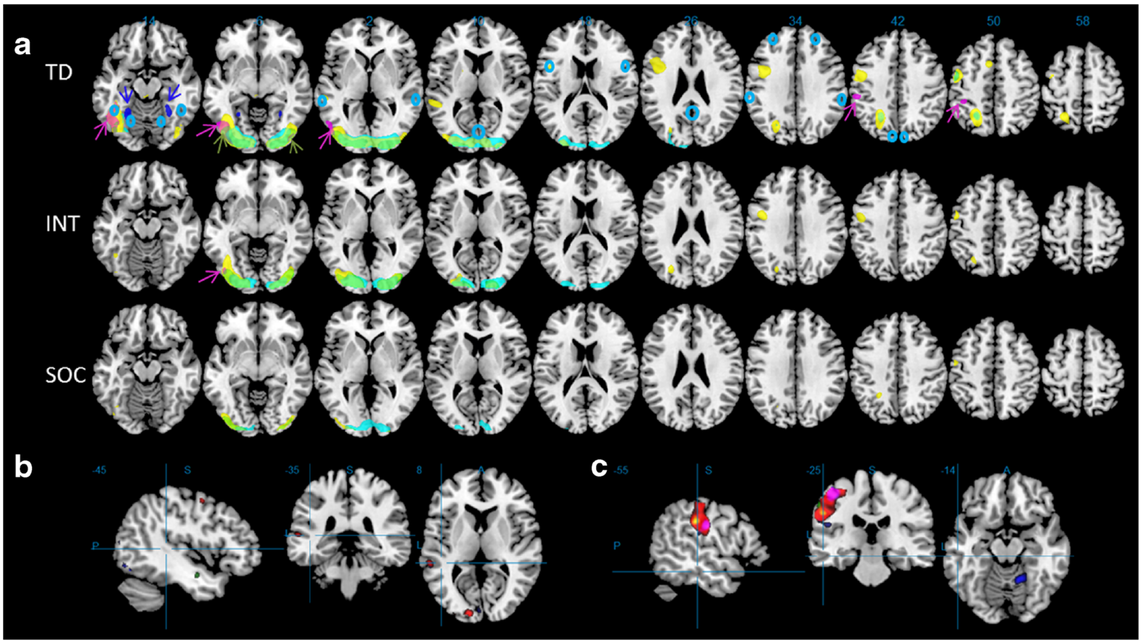

Fig. 1 FMRI Brain Activation for RAN. All the activation maps were thresholded at $p=0.05$ (FWE) and extent of 5 voxels. (**a**) Group activation for different stimuli>NULL are : *Color* (cyan), *Number* (green), and *Letter* (yellow). Significant task effects are indicated with color arrows: *Color*>*Number* (blue), *Number*>*Color* (olive), and *Letter*>*Color* (pink). No signficant differences for other differential contrasts were detected. Light blue circles on the TD map depict the ROIs. (**b**) Group Effects for TD>SOC (Red), TD>INT (blue), and INT>SOC (green); (**c**) Group Effects for TD<SOC (red), TD<INT (blue, overlapped with red in purple), and INT<SOC (green, overlapped with red in yellow). No group-by-task interaction was detected at the given threshold

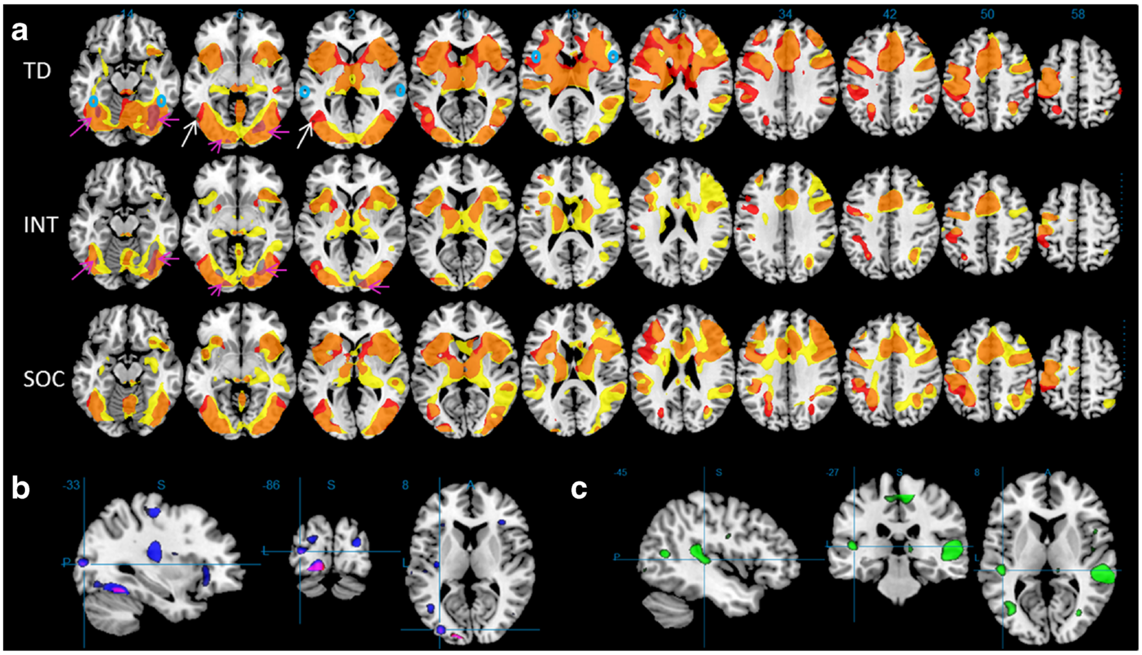

Fig. 2 FMRI Brain Activation for the CPT Task. All the activation maps were thresholded at p=0.05 (FWE) and extent of 5 voxels. (**a**) Group activation for stimuli>NULL conditions are: *Letter* (red) and *Face* (yellow). Significant task differences are indicated with colored arrows: *Face> Letter* (violet) , *Letter> Face* (white). Light blue circles on the TD map depict the ROIs. (**b**) Group Effects for TD>SOC (Red), TD>INT (blue), and INT>SOC (green); (**c**) Group Effects for TD<SOC (red), TD <INT (blue), and INT<SOC (green). No group-by-task interaction was detected at the given threshold

Window 0, 1, or 2. Sound Awareness was significantly higher for the INT group than for the SOC groups by the time of the 3rd fMRI (Time Window 3) by the Wilcoxon rank test and "At fMRI" by the GEE model (p=0.046). Compared to TD, both survivor groups scored significantly lower in Fluency (p<0.001); and the SOC group also scored significantly lower in Word Attack (p=0.02) and Sound Awareness (p =0.006) at the time of fMRI (Tables 3 and 4). GEE models showed no significant differences in longitudinal change among the groups. However, when each Time Window was examined

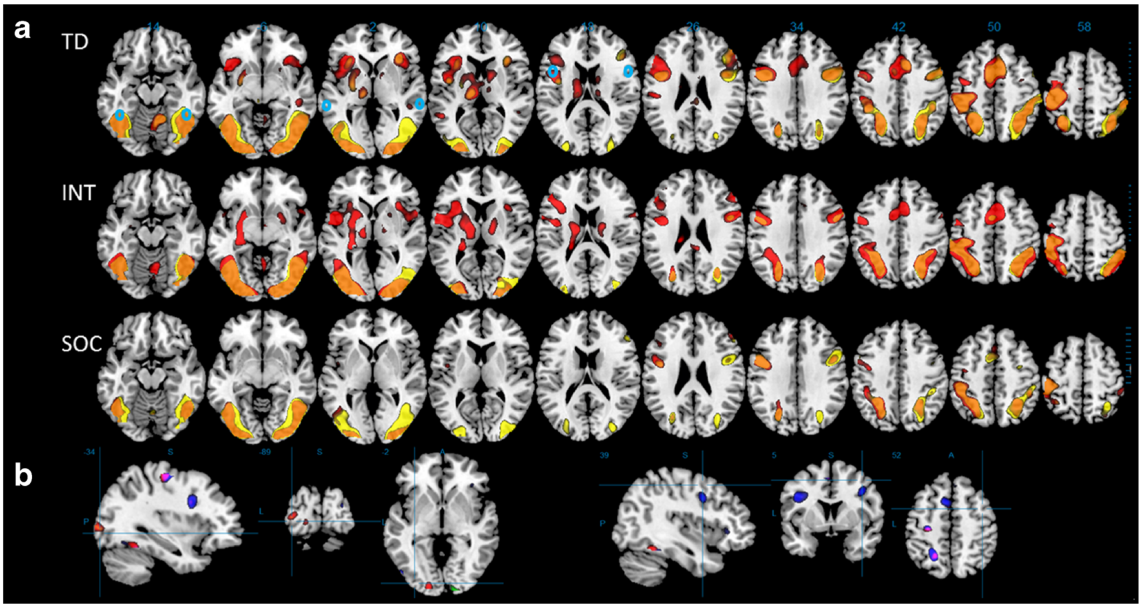

Fig. 3 FMRI Brain Activation for IMPLICIT READ. Activation maps were thresholded at p=0.05 (FWE) and extent of 5 voxels. Task conditions were to detect an ascender in a *Word* (red) or in a *False Font* string (yellow). There were no task differences, *Word> False Font* or *False Font> Word,* detected in any of the three groups. Light blue circles on the TD map depict the ROIs. B) Group Effects for TD>SOC (Red), TD>INT (blue), and INT>SOC (green). Other Group effects and group-by-task interations were not significant with the given threshold

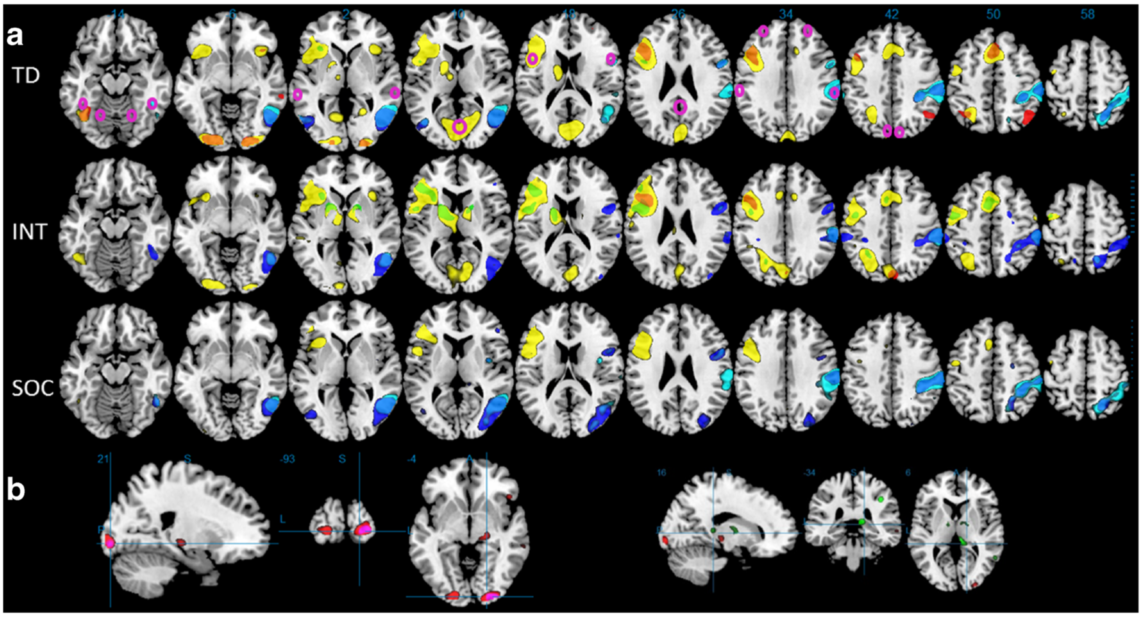

Fig. 4 FMRI Activation Maps for ORTHOPHONO Task. Activation maps were thresholded at $p=0.05$ (FWE) and extent of 5 voxels. Task differences: *Rhyme> Same Line* (yellow), *Rhyme> Same Letter* (green), *Same Line> Rhyme* (cyan), *Same Line> Same Letter* (blue), and *Same Letter> Same Line* (red). No significant effect detected for *Same Letter> Rhyme* condition in any of the group. Purple circles on the TD map depict the ROIs. (B) Group Effects for TD>SOC (Red), TD>INT (blue), and INT>SOC (green). Other Group effects and group-by-task interations were not significant with the given threshold

separately with Wilcoxon rank sum test, there was a declining trend for the reading scores in the survivors with years since completion of tumor treatment, except for the Sound Awareness score in the INT group. The group difference (INT vs. SOC) of score changes from baseline was marginally significant at Time Window 3 for Sound Awareness ($p=0.07$), but not for Fluency or Word Attack (Tables 3 and 4).

Brain activation Significant brain activation (p =0.05, Family Wise Error Corrected) for each of the five fMRI tasks

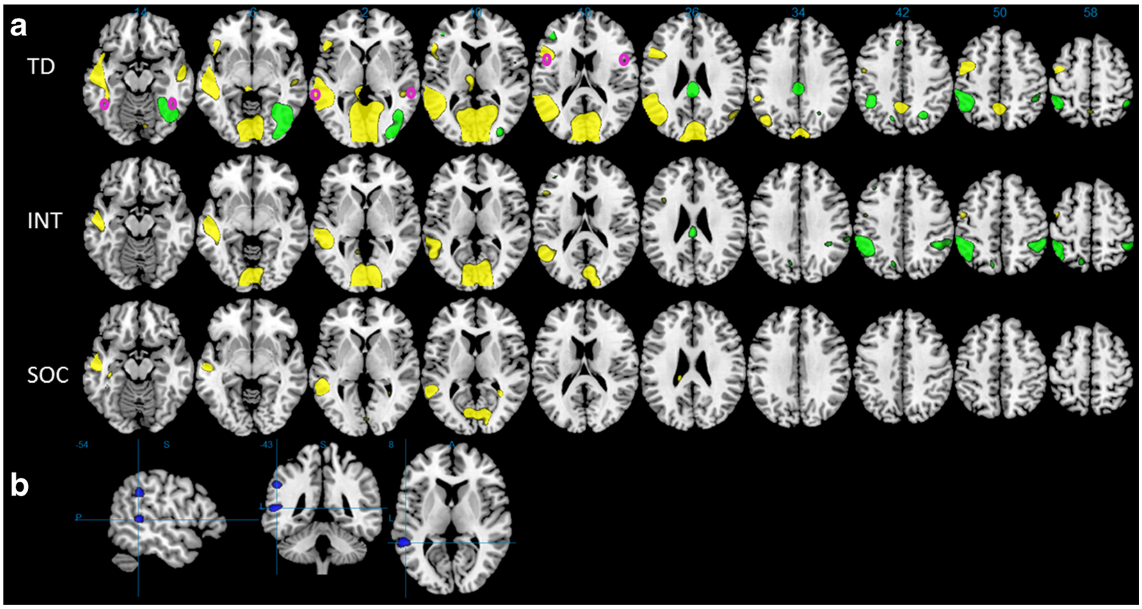

Fig. 5 FMRI Activaiton Maps for STORY READ Task. Activation maps were thresholded at $p=0.05$ (FWE) and extent of 5 voxels. *Story> False Font* (yellow) and *False Font> Story* (green). Purple circles on the TD map depict the ROIs. (B) Group Effects for TD>INT (blue). Other Group effects and group-by-task interations were not significant with the given threshold

Table 2 Number of participants assigned to each time window for reading scores and fMRI exams

Time window	Years after tumor treatment	N: Reading scores			N: fMRI exams		
		SOC	INT	TD	SOC	INT	TD
0	–	21	19	–	–	–	–
1	1–2	9	11	21	11	12	21
2	2–3	13	7	21	14	12	21
3	>3	9	8	21	13	13	21
At fMRI	2.5 [1.2 ,5.4]	16	16	21	21	19	21

Time Window 0: the baseline evaluation at SJMB03 protocol enrollment for Survivors, prior to reading intervention for the INT group

Time Window 1, 2, or 3: for survivors, the number reflects both the distribution of time since completion of therapy at study enrollment and the number of successfully completed evaluations; for TD, the numbers reflect the three fMRI protocol-based evaluations at 1 year intervals

At fMRI: the number refers to the total number of individuals with at least one successful evaluation during the course of the fMRI study

was detected in whole-brain random effects analysis, as described below. The reading-related contrasts of primary interest are listed in Table 5. In addition, we report all the combinations of task contrasts, group differences, and group and task interactions from the full factorial random effects analysis of the 5 fMRI tasks in the Supplementary Tables S1 to S5

For the RAN task (Fig. 1 and Table 1S), brain activation included left and right occipital-temporal regions for the three conditions, *Color, Number*, and *Letter,* in all three groups (Fig. 1a). With *Letter* stimuli, the TD group strongly activated a left hemisphere brain network typically involved in reading, including vOT, STS/MTG, IFG, parietal and occipital junction, and supplementary motor area. Activation in these regions was greater in the INT group than in the SOC group. Task effects (Fig. 1a) differentiating *Number* and *Color*, were only detected in TD, and included bilateral inferior occipital gyri for *Number> Color* and bilateral fusiform and lingual areas for *Color> Number.* Activation for *Letter> Color* was detected in left inferior occipital cortex for both TD and INT groups. The TD group also showed activation in left fusiform, inferior temporal, middle temporal, inferior and superior parietal, supramarginal and postcentral regions. Group effects included typical language areas in the left hemisphere for the *TD> INT* or *TD> SOC; and* left temporal region was significant for *INT> SOC* (Fig. 1b). Group effects were detected in left parietal region for *INT< SOC*, and left postcentral regions for *TD< INT* and *TD<SOC* (Fig. 1c). Detailed group differences for different stimuli are listed in Table 1S.

For the CPT task (Fig. 2 and Table 2S), all three groups activated similar regions for *Letter* or *Face condition*: left and right vOT, middle temporal, occipitoparietal, basal ganglia, and IFG. Activation in right vOT for *Face> Letter* detected in both TD and INT groups, and activation in left vOT detected for *Letter> Face* contrast only in TD group (Fig. 2a). Group effects were detected in the left inferior occipital for *TD> SOC* and *TD> INT,* and in bilateral temporal, parietal, and frontal regions for *TD> INT* (Fig. 2b). Group effects were also detected in left and right occipital, temporal, parietal and frontal regions for *INT< SOC* (Fig. 2c). Detailed group differences for different stimuli are listed in Table 2S.

During the IMPLICIT READ task (Fig. 3 and Table 3S), brain activation for *False-Font* was similar in the three groups, including right-lateralized vOT, bilateral occipitoparietal regions, pre- and post- central, supplementary motor area, and

Table 3 Reading scores of participants

Time window	SOC			INT			TD		
	Fluency	Sound awareness	Word attack	Fluency	Sound awareness	Word attack	Fluency	Sound awareness	Word attack
0	90(3.9)	96(2.8)	100(3.7)	94(2.7)	104(2.4)	101(3.0)	–	–	–
1	87(6.3)	107(5.6)	105(4.2)	95(2.5)	106(2.7)	102(3.0)	106(3.6)	111(3.2)	107(2.0)
2	89(4.4)	98(4.0)	100(4.6)	98(3.8)	105(3.9)	97(5.0)	107(3.5)	110(3.1)	111(2.2)
3	88(4.5)	95(2.5)	95(4.5)	93(3.0)	112(5.1)	98(2.9)	105(3.6)	116(2.9)	109(1.9)
At fMRI	89(4.9)	98(4.3)	99(3.9)	94(3.9)	108(3.8)	103(3.0)	111(3.2)	112(2.8)	110(1.5)

Time Windows 0 to 3: values are median (standard error)

At fMRI: values are estimated group means (standard error) from the Generalized Estimating Equation model

Table 4 P-values for reading score comparisons

Time window	SOC vs. TD			INT vs. TD			INT vs. SOC			Change from baseline		
	Fluency	Sound Awareness	Word attack	Fluency	Sound Awareness	Word attack	Fluency	Sound Awareness	Word attack	Fluency	Sound Awareness	Word attack
0	–	–	–	–	–	–	0.3	0.2	1	–	–	–
1	**0.02**	0.4	0.7	**0.007**	1	0.9	0.7	1	1	0.3	0.4	0.1
2	**0.003**	**0.02**	0.06	**0.03**	0.7	0.1	0.7	0.2	1	0.1	0.2	0.4
3	**0.001**	**0.003**	**0.01**	**0.001**	0.8	**0.009**	0.6	**0.04**	1	0.4	0.07	0.5
At fMRI	**<0.001**	**0.006**	**0.02**	**<0.001**	1	0.1	0.5	**0.046**	0.9	ns	ns	ns

All p values were Bonferroni corrected for multiple comparisons, and bold font highlights significant effects with $p < 0.05$

From *Time Windows* 0 to 3, Wilcoxon Rank Sum one-sided tests were used

For *At fMRI*, Generalized Estimating Equation was used to model group effect, which models the longitudinal data and properly accounts for missing evaluations and repeated measurement for individuals

bilateral IFG. Brain activation for *Word* was similar for the three groups in the vOT and occipitoparietal regions, but insula, cerebellum, thalamus, and putamen activation was detected only in the TD and INT groups (Fig. 3a). Group effects (Fig. 3b) were detected in left and right fusiform, occipital, and frontal, and left parietal regions for *TD> INT* and *TD> SOC*. Right calcarine and left middle occipital were detected for *INT> SOC*. Detailed group differences for different stimuli are listed in Table 3S.

During the ORTHOPHONO task (Fig. 4 and Table 4S), line judgment condition (contrasts *Same Line> Rhyme* and *Same Line> Same Letter*), all three groups (Fig. 4a) had similar activation in the right hemisphere: vOT, IFG, MTG, superior and inferior parietal gyrus, supra marginal gyrus, and superior and middle occipital gyrus. Left MTG was activated only in the TD and SOC groups. For contrast *Rhyme> Same Line*, Left IFG and supplementary motor area were activated in all three groups, but activations in bilateral vOT, left occipitoparietal, primary visual, and basal ganglia regions were detected only in TD and INT group. For *Rhyme> Same Letter,* left IFG, vOT, basal ganglia, supplementary motor, and inferior parietal regions were activated in the INT and TD groups. No activation was detected in the SOC group for *Rhyme> Same Letter* and *Same Letter> Same Line* contrasts. Group effects (Fig. 4b) were detected in right occipital and parietal regions for *TD> INT* and *TD> SOC*. In addition, left occipital, parietal, left and right fusiform, right frontal and middle temporal, and right thalamus were detected for *TD> SOC*. Right thalamus and MTG were also detected for *INT> SOC*. Detailed group differences for different stimuli are listed in Table 4S.

Finally, the STORY READ task (Fig. 5 and Table 5S) robustly activated brain regions typically involved in reading in all three groups (Fig. 5a), including left STG/MTG, left IFG, calcarine cortex for contrast *Story> False Font*. Activation in the TD group also included cuneus, precuneus, left thalamus, and pre- and post- central regions. For *False Font> Story*, parietal regions were activated in both INT and TD groups, but the right vOT was activated only in the TD group. No activation was detected in the SOC group for *False Font> Story*. Left MTG/STG, supramarginal gyrus, and cuneus were detected for TD>INT (Fig. 5b). Detailed group differences for different stimuli are listed in Table 5S.

ROI analysis The GEE models detected significant group effects of ROI activation for the contrasts of primary interest (Table 5, Fig. 6). Group differences of vOT activation *were* detected for stimuli Number (RAN), Face (CPT), and Word and False Font (IMPLICIT READING); and for contrasts *Letter> Color (*RAN), *Rhyme> Line* and *Letter> Line* (ORTHOPHONO), *Reading> FalseFont* (STORY READ). Group differences of STS/MTG activation *were* detected for stimuli Letter and Face (CPT), and Word (IMPLICIT READ

Table 5 Constrasts of primary interest in each fMRI task

fMRI task	Stimulus>NULL	Contrasts between stimuli
RAN	Letter, Number, Color	Letter>Number, Letter>Color
CPT	Letter, Face	Letter>Face
IMPLICIT READING	Word, False Font	Word>False Font
ORTHOPHONO	–	Rhyme>Line, Letter>Line
STORY READ	–	Reading>False Font

ING); and for contrasts *Letter> Color (*RAN), *Rhyme> Line* and *Letter> Line* (ORTHOPHONO), *Reading> FalseFont* (STORY READ). Group differences of IFG activation *were* detected for stimuli Letter and Number (RAN), Letter and Face (CPT), and False Font (IMPLICIT READING); and for contrasts *Letter> Number (*RAN), *Rhyme> Line* (ORTHOPHONO), *Reading> FalseFont* (STORY READ). Notably, a normative trend of the activation index for the INT group in vOT and STS/MTG during story reading (contrast *Story> False Font* of STORY READ), and in the STS/MTG ROI for orthographic and phonological judgments (contrasts *Same Letter> Same Line* and *Rhyme> Same Line* of ORTHOPHONO). Furthermore, during the STORY READ task, a clear trend of lateralized activation of the vOT across the three groups was also observed. Word Attack Scores were significantly associated with the activation in IFG during the STORY READ. No time effect for ROI activation was detected by the GEE models.

Discussion

The most salient findings of the study were that, years after completion of a computer-based intervention that targets

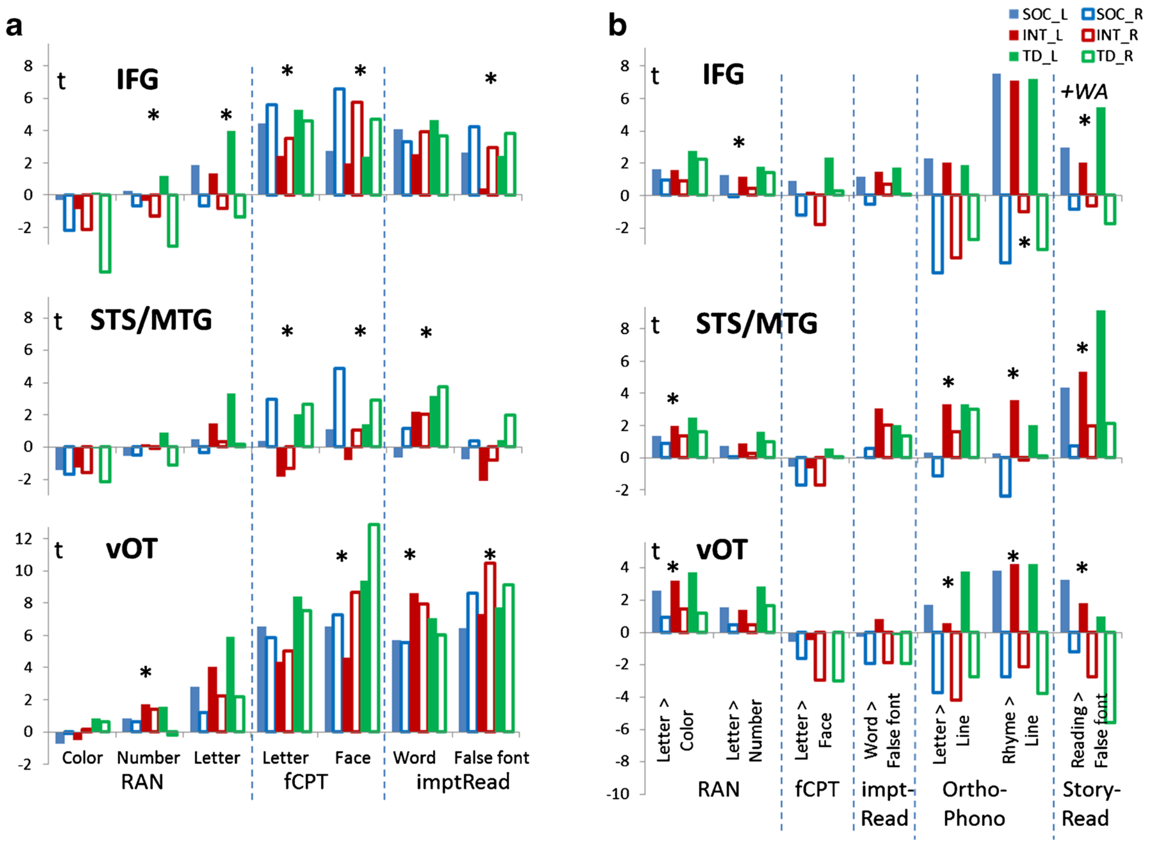

Fig. 6 Activation Index in the Three Regions of Interest. (**a**) Activation for different Stimuli (compare to NULL conditions), (**b**) Activation for different task contrasts. The GEE model identified significant group differences (marked with "*") in the activation of ROIs across fMRI tasks and contrasts. The GEE model also detected a sigificant positive associations between IFG activation and Word Attack score during Story Read (marked as "+ WA"). Significances were for $p<0.05$, FDR-corrected. IFG, inferior frontal gyrus; STS/MTG, superior temporal sulcus / middle temporal gyrus; and vOT, ventral occipital temporal gyrus. INT, reading intervention medulloblastoma survivors ; SOC, standard-of-care medulloblastoma survivors on; TD, typically developing children

phonological aspects of reading and language, Sound Awareness scores were better in intervention participants than in the survivors in the standard-of-care control group and that brain activation across a battery of reading-related tasks differed among the groups in a pattern that suggests a normative trend of some neural systems for reading in the INT group.

Reading scores

Consistent with the behavioral outcomes from the original reading intervention trial (Palmer et al. 2014), we did not find any difference in decoding skills (Word Attack score) between the INT and SOC groups, in the subset of patients who participated in the fMRI study. Phonological skills were not analyzed for the overall group (Palmer et al. 2014), but at the time of fMRI, the INT survivors had significantly higher Sound Awareness scores, and their Sound Awareness scores did not show the declining trend observed in the SOC survivors. Baseline Sound Awareness scores for the INT group were not significantly higher than SOC, but the full GEE model did not detect significant differences of longitudinal changes among the groups. The marginal group difference in Sound Awareness score changes from baseline to Time Window 3 provides evidence of an intervention effect. Overall, the reading scores suggest an apparent preservation of the phonological skills in the INT survivors. This effect is consistent with the theoretical foundations of the Fast ForWord program, which emphasizes sound discrimination and phonological processing (Gillam et al. 2008; Loeb et al. 2009). Our finding of differences in phonological skills but not reading fluency is similar to the findings from studies of Fast ForWord intervention in children with language impairment (Gillam et al. 2008; Loeb et al. 2009). Children with medulloblastoma may have typical neural systems for reading prior to tumor growth, diagnosis, and treatment. Alternatively, brain networks may have been disrupted by embryonal tumor development and/or treatment such that neural systems for reading are disrupted in unique ways, and in turn respond to intervention differently than typically developing children or children with other kinds of reading difficulties.

FMRI results

Four of the five fMRI tasks, RAN, IMPLICIT READ, ORTHOPHONO, and STORY READ, required language- and reading-related skills in the areas of letter recognition, word recognition, phonological processing, orthographic processing, and semantic processing through naming, rhyming, and story comprehension. The CPT task demanded sustained attention and contrasted simple letter and face recognition. In the TD group, these fMRI tasks activated occipital, temporal, parietal and frontal areas known to have a key role in reading and its development (Price 2012). Overall, the activation maps of the INT group more resembled those of the TD group than the maps of SOC group during the four language tasks, RAN, IMPLICIT READ, ORTHOPHONO, and STORY READ, while there was little difference in activation among the three groups during the CPT task, which primarily is a test of attention. This overall group activation pattern suggests an intervention effect, with the INT survivors engaging a more typical brain network during reading-related tasks. Additional evidence for an intervention effect was apparent among the contrasts within the ORTHOPHONO task. Contrasts for line orientation judgment (*Same Line> Same Letter* or *Same Line> Rhyme*) showed comparable activation for all three groups in the right hemisphere, while contrasts for letter identification (*Same Letter> Same Line*) or rhyming effects (*Rhyme> Same Letter* and *Rhyme> Same Line*) revealed activation in the left hemisphere language areas and sub-cortical areas in the INT and TD groups but not in the SOC group.

Regions of Interest

vOT We had hypothesized that focal deficits in the vOT might account for early visual letter or word recognition difficulties that lead to reading deficits in medulloblastoma survivors, because of its proximity to tumor site/radiation volume. The vOT was reliably activated to different stimuli (compare to NULL condition) in our battery of fMRI tasks. Thus, activation of vOT was not diminished in the survivors. However, there were group differences of vOT activation and a normative trend of activation and lateralization for the INT group during task conditions that required more demanding reading-relevant processing, such as rhyming in ORTHOPHONO and story comprehension in STORY READ. Since the responses of the left vOT are not exclusive to word form recognition (Price and Devlin 2011; Turkeltaub et al. 2008) and the activation of vOT during reading reflects integration of word visual features with phonological and semantic information represented in temporoparietal and frontal language areas (Kherif et al. 2011; Price 2012), thus, we suggest the brain of INT survivors may recruit a more typical neural network that engages ventral visual processing to support reading.

MTG/STG The posterior part of middle temporal gyrus and superior temporal sulcus is reported to activate for meaningful sentences and is thought to integrate sound and meaning and to consolidate semantic concepts (Price 2012; Pugh et al. 2013). Activation at left STS/MTG regions increased in children with dyslexia at the completion of phonologically-based reading interventions (Gebauer et al. 2012; Shaywitz et al. 2004; Temple et al. 2003). Consistent with these studies, we also found that activation in left STS/MTG ROI increased as the fMRI tasks required more phonological or semantic processing, and the lateralization of STS/MTG activation during the ORTHOPHONO and STORY READ tasks was more like the typically developing children for the INT group than for the SOC group (Fig. 6). The activation patterns in the temporal region across the tasks and among the groups again suggested that the phonological processing during reading may be better preserved or strengthened in the INT group.

IFG The left IFG has well-established roles in language processing: it is more active for new or irregularly spelled words than for familiar frequent words; and in adult or skilled readers it asserts top – down modulation on information pathways of phonological or orthographic processes via occipitotemporal or temporoparietal regions (Bitan et al. 2006; Price 2012; Pugh et al. 2013). The correlation of IFG activation with Word Attack scores in our participants may reflect a synergistic role of IFG in phonic, decoding, and semantic processes. Activation in the IFG was altered in medulloblastoma survivors, but no intervention effect was detected in the ROI. This may reflect the late maturation of frontal lobes during normal development (Romine and Reynolds 2005) and the weaker top-down IFG modulation on reading networks in children (Bitan et al. 2006). It is also possible that the phonologically biased Fast ForWord reading intervention had limited effects on frontal activation, consistent with the low scores in Fluency and Word Attack in both INT and SOC groups.

Subcortical regions There is growing recognition of the critical role of cortical-subcortical interactions in complex human cognition and subcortical roles in high level language learning and processing (Booth, Wood, Lu, Houk, and Bitan 2007; Friederici 2006; Ketteler, Kastrau, Vohn, and Huber 2008; Pugh et al. 2013; Seghier and Price 2010). Robust subcortical activation in the CPT for all three groups was detected, while a similar CPT task activated fewer subcortical regions in adults (Ogg et al. 2008). This is consistent with the notion that subcortical regions are more activated during procedure learning (including language) and in children developing reading skills (Friederici 2006; Pugh et al. 2013). During word reading (IMPLICIT READ) and rhyming (ORTHOPHONO), caudate, putamen, and thalamus activations were detected in the TD children and INT survivors, but not in the SOC survivors. The more typical pattern of basal ganglia and thalamus activation in the INT survivors may indicate improved dynamics of subcortical and cortical connectivity in the INT group during rhyming judgments and implicit word reading. However this gain may not be generalized, as left thalamus activation during STORY READ was detected in the TD children but not in the two survivor groups.

Limitations

Our analysis was based on behavioral testing and imaging data that were acquired as part of a larger study of neural systems for reading in children treated for medulloblastoma. The post-hoc analysis of only a subsample of intervention participants, with some missing evaluations in the survivors, limited the sensitivity of our study to evaluate many factors that may have affected the survivors reading abilities and responsiveness to reading intervention. Though there were no significant differences in the clinical and demographic characteristics of the survivor groups, it will be important to clarify the interactions of these factors (e.g., radiation dose, socioeconomic status) with response to prophylactic intervention.

Summary

Improved Sound Awareness scores and an apparent normative trend in brain activation patterns for reading-related tasks in the INT survivors suggest sustained neural and behavioral effects of prophylactic intervention administered during medulloblastoma treatment. Even though the observed neural effects and improved Sound Awareness scores may not be associated with generalized improvement in reading skills at the time of fMRI, the results provide important evidence for potential benefits of prophylactic intervention. The long-term real-life effects of improved phonological skills on reading abilities in medulloblastoma survivors are currently unknown. Future research with functional neuroimaging in this population may help to understand the causes of their cognitive deficits, clarify the neural mechanisms of successful remediation, and identify neural phenotypes of children most likely to benefit from a given approach to intervention.

Acknowledgments This work was supported by the Cancer Center Support (CORE) grant CA21765 from the National Cancer Institute, grant HD049888 from the National Institute for Child Health and Human Development, grant RR029005 from the National Center for Research Resources, and by ALSAC.

Conflict of interest Ping Zou, Heather M. Conklin, Matthew A. Scoggins, Yimei Li, Xingyu Li, Melissa M. Jones, Shawna L. Palmer, Amar Gaggar, and Robert J. Ogg declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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