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Cognitive Performance, Aerobic Fitness, Motor Proficiency and Brain Function among Children Newly Diagnosed with Craniopharyngioma

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Abstract

Objective: Craniopharyngioma survivors experience cognitive deficits that negatively impact quality of life. Aerobic fitness is associated with cognitive benefits in typically developing children and physical exercise promotes recovery following brain injury. Accordingly, we investigated cognitive and neural correlates of aerobic fitness in a sample of craniopharyngioma patients.

Method: Patients treated for craniopharyngioma [$N=104$; 10.0 ± 4.6 years; 48% Male] participated in fitness, cognitive and fMRI ($n=51$) assessments following surgery but prior to proton radiation therapy.

Results: Patients demonstrated impaired aerobic fitness [peak oxygen uptake ($PKVO_2$) = 23.9 ± 7.1 ; 41% impaired (i.e., 1.5 SD < normative mean)], motor proficiency [Bruininks-Oseretsky (BOT2) = 38.6 ± 9.0 ; 28% impaired] and executive functions (e.g., WISC-IV Working Memory Index (WMI) = 96.0 ± 15.3 ; 11% impaired). $PKVO_2$ correlated with better executive functions (e.g., WISC-IV WMI $r=.27$, $p=.02$) and academic performance (WJ-III Calculation $r=.24$, $p=.04$). BOT2 correlated with better attention (e.g., CPT-II omissions $r=.26$, $p=.04$) and executive functions (e.g., WISC-IV WMI $r=.32$, $p=.01$). Areas of robust neural activation during an n-back task included superior parietal lobule, dorsolateral prefrontal cortex, middle and superior frontal gyri ($p<.05$, corrected). Higher network activation was associated with better working memory task performance and better BOT2 ($p<.001$).

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Conclusions: Prior to adjuvant therapy, children with craniopharyngioma demonstrate significantly reduced aerobic fitness, motor proficiency and working memory. Better aerobic fitness and motor proficiency are associated with better attention and executive functions, as well as greater activation of a well established working memory network. These findings may help explain differential risk/resiliency with respect to acute cognitive changes that may portend cognitive late effects.

Keywords

pediatric; brain tumor; cognitive late effects; fMRI; acquired brain injury; exercise

Childhood brain tumor survivors are at significant risk for cognitive impairments that are associated with decreased academic and vocational attainment, as well as a reduced quality of life (Castellino, Ullrich, Whelen, & Lange, 2014; Mitby et al., 2003; Mostow, Byrne, Connelly, & Mulvihill, 1991; Mulhern & Butler, 2004; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004). With a growing survivor population, efforts to improve long-term cognitive outcomes become imperative. Longitudinal trials of children treated for brain tumors reveal declines on global cognitive measures that reflect a failure to learn new skills at the same rate as healthy peers (Mulhern et al., 2004; Palmer et al., 2001). Emerging research suggests impairments in attention, working memory and processing speed may be proximal contributors to these global declines (e.g., Castellino et al., 2014; Krull, Hardy, Kahalley, Schuitema, & Kesler, 2018; Schatz, Kramer, Ablin, & Matthay, 2000; Ullrich & Embry, 2012). Risk factors for cognitive deficits have most consistently included younger age at treatment, longer time since treatment, higher treatment intensity, female gender and complicating medical factors (e.g., stroke or meningitis; Castellino et al., 2014; Krull et al., 2018; Mulhern et al., 2004; Ullrich & Embry, 2012). Even after accounting for these risk factors, there is variability in cognitive outcomes among brain tumor survivors that suggests the presence of protective factors for some. The greater childhood acquired brain injury literature suggests protective factors might include genetic factors (e.g., allelic variants of apolipoprotein E), pre-injury factors (e.g., higher premorbid cognitive ability or better behavioral adjustment) and contextual factors (e.g., higher socioeconomic status or better family functioning; see Yeates, Levin, & Ponsford, 2017).

Craniopharyngioma is a slow growing, extra-axial tumor located in the sella/suprasellar brain region. While craniopharyngiomas are rare, 30–50% are diagnosed during childhood, with a peak onset between 5 and 14 years of age (Muller et al., 2011; Ozyurt et al., 2014). Prognosis is very good with overall survival rates greater than 80% at ten years post diagnosis (Poretti, Grotzer, Ribi, Schonle, & Boltshauser, 2004). While craniopharyngiomas are benign in histology, they can be difficult to manage medically given their neuroanatomical location. Long-term morbidity is associated with tumor and treatment effects on surrounding structures including: endocrinopathies, sleep disturbance and decreased fitness due to hypothalamic/ pituitary damage; visual disturbance due to mass effect on the optic chiasm; and memory impairment due to disruption of Papez circuit including the mammillary bodies (Fournier-Goodnight et al., 2017; Muller et al., 2011; Ozyurt et al., 2014). Of particular relevance to the current study, prior research has shown a significant proportion of children surgically treated for craniopharyngioma have aerobic

fitness lower than healthy peers, even when appropriately treated with growth hormone replacement (Piquel et al., 2012). Consensus is lacking regarding the optimal treatment approach for pediatric craniopharyngioma, with some medical teams preferring gross total resection and others preferring limited surgery followed by radiation therapy (Muller, 2017). While surgery and/or radiation therapy are often required for disease control, both are associated with cognitive risk (Poretti et al., 2004). Typically, survivors of childhood craniopharyngioma demonstrate intact intellectual functioning with deficits noted in sustained attention (Fjalldal et al., 2013; Ozyurt et al., 2014), processing speed (Fjalldal et al., 2013; Waber et al., 2006), and learning and memory (Fjalldal et al., 2013; Ondruch, Maryniak, Kropiwnicki, Roszkowski, & Daszkiewicz, 2011; Ozyurt et al., 2014). Poorer performance has been associated with hypothalamic involvement of the tumor (Fjalldal et al., 2013; Ozyurt et al., 2014;), hydrocephalus, cerebrospinal fluid diversion procedures, and younger age at irradiation (Di Pinto, Conklin, Li, & Merchant, 2012).

The medical benefits of aerobic exercise are well established for the general population including decreased risk for metabolic, cardiovascular and metastatic disease (Powell & Blair, 1994). Cognitive benefits of exercise are emerging with evidence to suggest improvements in learning and memory (Winter et al., 2007), delayed age-related memory decline or neurodegenerative disease (Friedland et al., 2001; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), and promotion of recovery following acquired brain injury (Devine & Zafonte, 2009). Research using murine models has provided clues regarding underlying mechanisms for exercise-related cognitive benefits including neurogenesis, synaptic plasticity, angiogenesis and enhanced neurotransmitter function (Farmer et al., 2004; Chaouloff, 1989; van Praag, Christie, Sejnowski, & Gage, 1999).

Correlational studies indicate children of higher aerobic fitness outperform lower fit children on cognitive, academic and real world problem solving tasks (Chaddock, Hillman, et al., 2012; Fedewa & Ahn, 2011; Pontifex et al., 2011). Further, higher fit children may have larger regional brain volumes in the basal ganglia (Chaddock, Erickson, Prakash, VanPatter, et al., 2010) and hippocampus (Chaddock, Erickson, Prakash, Kim, et al., 2010), which could mediate the relationship between fitness level and learning. An association in children between aerobic fitness and greater efficiency of neural networks underlying executive functions has also been revealed by fMRI studies (Chaddock, Erickson, et al., 2012; Voss et al., 2011). There are relatively few exercise intervention studies with children, with most targeting obesity and some revealing cognitive benefits (Castelli, Hillman, Hirsch, Hirsch & Drollette, 2011; Davis et al., 2007; Davis et al., 2011; Donnelly et al., 2009). For example, Davis and colleagues conducted a randomized controlled trial of school age children and found an effect of daily exercise on executive function and math achievement. There was also evidence of increased neural activity in bilateral prefrontal cortices in the exercise group compared to controls (Davis et al., 2007; Davis et al., 2011). Multiple studies suggest aerobic exercise may influence executive functions in particular (e.g., Chaddock, Erickson, et al., 2012; Chaddock, Hillman, et al., 2012; Davis et al., 2007; Davis et al., 2011).

In the current study, we evaluated a group of children diagnosed with craniopharyngioma following surgical resection but prior to adjuvant radiation therapy. Our primary goal was to investigate cognitive and neural correlates of aerobic fitness in order to detect differential

risk/resiliency for acute cognitive changes that might portend late effects and identify targets for intervention. Based on the existing literature, we hypothesized: children would have significantly reduced aerobic fitness and motor proficiency at this point in treatment; children with higher fitness would exhibit better executive functioning (i.e., sustained attention, working memory, verbal fluency and behavioral inhibition); and better performance on working memory measures would correlate with greater activation of related neural networks as revealed by fMRI.

Method

Participants

All study participants were patients enrolled on a phase II trial of limited surgery and proton therapy (PT), or observation after radical resection (RT2CR; NCT01419067). Participants were infants through 21 years of age, newly diagnosed with craniopharyngioma by histology, cytology or neuroimaging. Children were excluded from participation for a history of treatment with fractionated radiation therapy, intracystic P-32, intracystic bleomycin or radiosurgery, and if pregnant. Those under two years of age, with limited English proficiency, premorbid neurological (e.g., traumatic brain injury) or neurodevelopmental (e.g., Down syndrome) conditions did not receive protocol-based cognitive evaluations. This study was conducted at St. Jude Children's Research Hospital between August 2011 and May 2016 as approved by the Institutional Review Board; the study was completed in accordance with the Helsinki Declaration and written informed consent was obtained prior to participation.

Procedure

Cognitive Assessment.

Patients participated in baseline cognitive assessments after surgery but prior to initiation of PT. All utilized cognitive measures have age-specific norms from representative standardization samples, and demonstrated reliability and validity. Intellectual ability was assessed using an 8 subtest pro-rated IQ from an age appropriate Wechsler scale [Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) for children age 6 to 16 years; Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler 2008) for children 17 years]. These measures provide an age-standardized score with mean of 100 and standard deviation of 15. Based on the existing aerobic fitness and exercise literature, additional cognitive measures were selected for this study from the larger protocol battery to assess attention, executive functions and academic skills.

The Conners' Continuous Performance Test-Second Edition (CPT-II; Conners, 2004) is a computerized measure of sustained attention. Letters are presented one at a time on a computer screen and the participant presses the space bar as quickly and accurately as possible for any letter except the letter "X". The CPT-II program computes an omission score (index of inattention), commission score (index of impulsivity), and hit reaction time (index of processing speed). Scores are age-standardized T-scores with mean of 50 and standard deviation of 10.

Selected executive function measures included the Working Memory Index (WMI) from the age appropriate Wechsler Scale, comprised of the Digit Span and Letter-Number Sequencing subtests. Digit Span includes Digit Span Forward (participant repeats digits verbatim) and Digit Span Backward (participant repeats digits in reverse order). For Letter-Number Sequencing, the examiner presents sequences of numbers and letters after which the participant repeats the numbers in ascending order followed by the letters in alphabetical order. Retrieval Fluency from the Woodcock-Johnson Test of Cognitive Abilities, Third Edition (WJ-III; Woodcock, McGrew & Mather, 2001) was selected as a measure of verbal fluency that requires the participant to name as many exemplars of a provided category as they can in one minute. The Color-Word Interference Test from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan & Kramer, 2001) was selected as a measure of behavioral inhibition. For this task, the participant must inhibit a pre-potent response (reading a color name) for a more challenging response (naming the incongruent ink color of the color name). Finally, parents completed the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000), a parent questionnaire consisting of 86 items rated as occurring “never, sometimes or often”. The Working Memory (WM) Scale, Behavior Regulation and Metacognitive Indices (BRI/MCI), and the Global Executive Composite (GEC) were chosen as scores of interest. All scores are age standardized. The Wechsler WMI and WJ-III Retrieval Fluency have a mean of 100 and standard deviation of 15. The D-KEFS Color Word Interference has a mean of 10 and standard deviation of 3. The BRIEF has a mean of 50 and standard deviation of 10, with higher scores indicative of more problems.

To assess academic skills, we selected two subtests from the Woodcock Johnson Tests of Academic Achievement- Third Edition (WJ-III; Woodcock, McGrew & Mather, 2001). The Letter-Word Identification subtest requires basic letter recognition followed by single word reading. The Calculation subtest requires completion of simple to complex mathematical computations based on age. Both of these subtests produce an age standardized score with a mean of 100 and standard deviation of 15.

Fitness Assessment.

The Bruinicks-Oseretsky Test of Motor Proficiency, Second Edition (BOT2; Bruininks & Bruininks, 2005) was administered by an exercise physiologist as a norm-referenced measure of gross and fine motor skills. The motor composite score from this measure captures fine motor control, manual coordination, body coordination, strength and agility. The score is age standardized with a mean of 50 and a standard deviation of 10. Internal consistency reliability (.95-.96) and inter-rater reliability (.98) coefficients are extremely high for the study age range. Criterion oriented validity has also been demonstrated with a high correlation between the BOT2 and the Peabody Developmental Motor Scales (.73).

Peak oxygen uptake ($PKVO_2$) was calculated as a measure of aerobic fitness. Participants completed a graded maximal exercise test using a cycle ergometer. During this test, concentrations of oxygen and carbon dioxide of inhaled and exhaled air were measured using a MedgraphicsUltima Cardio 02® metabolic testing system that collects breath-by-breath measurements via a face mask. $PKVO_2$ represents oxygen consumption when the

participant can go no further. It is measured in ml/kg/min, accounting for body size. Average time on the cycle ergometer was 7 minutes, 51 seconds and correlated with age ($r=.63$, $p<.001$). Gender- and body size-based norms were used to derive predicted PKVO₂ scores for comparison with patient performance (James et al., 1980).

Neuroimaging.

The fMRI examination was designed to explore neural correlates of WM performance in relation to fitness indicators. Neuroimaging was completed during baseline, prior to PT. Before scanning, participants watched a presentation about scanning procedures, practiced fMRI tasks and tried the manual response mechanism. All scans were completed on 3 Tesla Magnets (Trio and Skyra models, Siemens Medical Systems). Conventional MRIs were used to identify morphologic abnormalities, facilitate spatial normalization of brain images, and visualize fMRI results. Whole brain functional images were acquired with T2*-weighted EPI pulse sequences (TR= 2 s, TE= 30 ms, FOV= 192 mm, matrix= 64 × 64, bandwidth= 2055 Hz/pixel, 32 slices, slice thickness= 3.5 mm).

During fMRI, participants completed a sensorimotor task (visual, auditory, and motor stimulation) and a verbal n-back working memory task used in prior studies with healthy adults (Jacola et al., 2015). During the sensorimotor survey, participants viewed an alternating checkerboard, heard a series of ascending and descending tones, and were asked to tap their fingers while the checkerboard was visible. Sensory blocks were interleaved with periods of rest with a simple fixation cross (Zou et al., 2011). For the n-back working memory task, participants viewed a continuous stream of phonologically distinct letters presented one at a time on a computer screen. Participants were instructed to respond when the currently presented letter was identical to the letter presented at the specified interval (1- or 2-back). There was a 0-back control condition during which participants always responded to a pre-determined letter (e.g., X). Stimuli were presented at the back of the magnet with an LCD projector and viewed via a mirror on the head coil.

Data Analytic Plan

To characterize the sample, descriptive statistics of demographic and clinical variables were calculated. One-sample Z-tests were used to investigate how the sample differed from the normative population at baseline on measures of cognition, aerobic fitness and motor proficiency. Given there is no large scale PKVO₂ normative data for computation of a Z-test, a one sample t-test was used to compare observed performance to predicted performance using body size and gender-based norms (James et al., 1980). Correlations were conducted to examine relationships among clinical, cognitive, aerobic fitness and motor proficiency measures. All p-values were two-sided. Analyses were implemented in SAS 9.4.

Neuroimaging analysis targeted three areas: 1) patterns of activation during completion of a sensorimotor survey and the n-back working memory task to establish relative rest and task-related activity in this sample, 2) associations of neural activation and n-back accuracy to identify activation patterns associated with better working memory performance, and 3) associations of neural activation and fitness/motor proficiency indicators to identify activation patterns associated with higher fitness. Functional images were analyzed with

Statistical Parametric Mapping (SPM) via a 2-level analysis. In the first-level analysis, data were analyzed according to a fixed-effect generalized linear model with task-induced activity represented by a boxcar function convolved with canonical hemodynamic response function. Contrasts selecting for activation of interest were set in a model and contrast images from each participant were used as a variable in a second-level, random-effects analysis. For the n-back task, the contrast of interest was 2-back > 0-back given anticipation of greater variability in performance on the 2-back condition that would optimize sensitivity to performance-related effects.

Results

Demographic and Clinical Characteristics

Sample characteristics are reported in Table 1. The group was on average 10 years of age, balanced by gender (48% male) and largely Caucasian (65%). The majority of patients underwent tumor resection (72%). Prior to baseline study assessments, patients underwent an average of 1.5 cranial surgical procedures (median = 1; range 0 – 8), with 33% requiring cerebral spinal fluid diversion and 53% experiencing diabetes insipidus (DI). Based on body mass index (BMI), 24% of the sample was overweight (BMI > 25) and 15% were obese (BMI > 30).

Cognitive Performance, Motor Proficiency and Aerobic Fitness

Performance of this sample on the full cognitive battery administered at baseline has been previously reported (Fournier-Goodnight et al., 2017). For the smaller set of cognitive variables selected for this study, one sample Z-tests indicate the sample performed significantly worse than normative expectations on measures of attention regulation (CPT-II omissions- 52.4 ± 14.4 , $p=0.049$, effect size [*Cohen's d*]=0.240), working memory (Wechsler WMI- 96.0 ± 15.3 , $p=0.016$, $d=0.267$; BRIEF WM scale- 52.6 ± 11.7 , $p=0.012$, $d=0.255$) and verbal fluency (W-JIII Retrieval Fluency- 95.0 ± 15.8 , $p=0.002$, $d=0.336$). However, they were significantly less impulsive than normative expectations (CPT-II commissions- 46.8 ± 10.1 , $p=0.009$, $d=0.318$). All other investigated cognitive variables were within the range of normative expectations. One-sample Z-tests indicated the group demonstrated significantly worse motor skills than normative expectations on the BOT2 (38.6 ± 9.0 , $p<0.001$, $d=1.138$). A one sample t-test revealed significantly worse aerobic fitness than normative expectations as measured by PKVO₂ (-11.54 ± 8.22 , $p<0.001$, $d=1.403$).

Correlations among demographic/clinical variables with cognitive and fitness measures indicate that older age was significantly associated with higher PKVO₂. Female gender was significantly associated with developing DI and worse PKVO₂. A higher number of surgical procedures was significantly associated with developing DI, worse PKVO₂ and worse BOT2 performance. A greater extent of surgical resection was significantly associated with developing DI, worse PKVO₂ and worse attention regulation (CPT-II Omissions, CPT-II Commissions). DI was associated with worse PKVO₂ and BOT2. Higher BMI was associated with worse PKVO₂. PKVO₂ and BOT2 were significantly correlated ($n=82$, $r=0.43$, $p<0.001$). See Table 2.

Correlations among fitness indicators and cognitive measures indicated better PKVO₂ was significantly associated with better working memory (Wechsler WMI), verbal fluency (WJ-III Retrieval Fluency) and mathematics (WJ-III Calculation). Better BOT2 performance was associated with higher IQ (Wechsler IQ), better attention regulation (CPT-II Omissions; CPT- Hit RT), better working memory (Wechsler WMI), better verbal fluency (WJ-III Retrieval Fluency) and better parent reported executive functions (BRIEF MCI, BRIEF BRI). When accounting for multiple comparisons using the False Discovery Rate (Benjamini & Hochberg, 1995), within measures, two of the three significant correlations between PKVO₂ and cognitive variables remained significant and five of the seven significant correlations between BOT2 and cognitive variables remained significant. See Table 3 for a summary of correlations.

Neuroimaging Findings

Fifty-one of the 104 study participants participated in fMRI examination with usable data. Reasons for not participating included: less than 8 years of age ($n=38$), anxiety/claustrophobia ($n=3$), vision impairment ($n=6$) and patient refusal ($n=2$). Data for an additional four patients were excluded due to shunt artifact ($n=2$), braces artifact ($n=1$) and poor slice positioning ($n=1$). Comparison of those with and without useable fMRI exams revealed the group with exams was significantly older (13.1 ± 3.2 vs. 7.0 ± 3.5 , $p < 0.001$), consistent with greater challenges conducting non-sedated MRI exams with younger children. There were no significant differences between groups in gender, race, and rate of surgical resection, use of CSF diversion or DI status.

The sensorimotor survey task revealed a pattern of brain activity consistent with known sensory and motor cortex (Table 4; Figure 1). Robust activation was detected along the calcarine sulcus and extended into the fusiform, lingual and middle occipital gyri known for vision processing. Task activation was also located in the superior temporal gyrus and pre-central gyrus known for primary auditory and motor processing, respectively. Additional activation was detected in cingulum cortex known to be associated with attention (Ogg et al., 2008). Activity in part of the left precuneus was positively associated with higher PKVO₂ ($p < 0.05$, FWE corrected). Additionally, higher brain activation in right insula, left superior temporal and supramarginal areas was associated with higher BMI ($p < 0.05$, FWE corrected). There were no associations between activity during the sensorimotor survey and BOT2 performance, gender or DI status.

The pattern of activation in the n-back task (Table 4; Figure 2) was consistent with the neuroimaging literature (Nee & Brown, 2013; Owen, McMillan, Laird, & Bullmore, 2005). Analysis identified robust activation in bilateral superior parietal lobule, dorsolateral prefrontal cortex, and middle and superior frontal gyri ($p < 0.05$, FWE corrected). Decreased activation in posterior regions within the working memory network were associated with increasing commission errors ($p < 0.05$, FWE corrected). Activity in anterior areas within the working memory network were positively associated with BOT2 scores ($p < 0.05$, univariate analysis, FWE corrected). All associations controlled for age except the BOT2 association falls just below significance ($p < 0.1$, FWE corrected) with age in the model. However, this

sub-threshold pattern was consistent across all models tested. There were no associations between activity during the n-back task and PKVO₂, gender or DI status.

Discussion

Consistent with our first hypothesis, study findings indicate children with craniopharyngioma demonstrate worse than expected performance prior to adjuvant therapy not only in cognitive abilities (sustained attention, working memory, and verbal fluency) but also motor proficiency and aerobic fitness. Interestingly, better motor proficiency and aerobic fitness were associated with better attention regulation, executive functions and academic performance. Further, better motor proficiency and better working memory performance were associated with greater activation of frontal and parietal areas, respectively, of a well established fMRI working memory network. Of note, female participants were more likely to develop endocrinopathies and to have worse aerobic fitness. More surgical procedures and greater extent of surgery were also associated with endocrinopathies and worse fitness, as well as worse performance on attention measures.

Given the suprasellar location of craniopharyngioma, it is not surprising that tumor mass effect and/or surgical intervention could result in endocrinopathies and physical deconditioning prior to adjuvant, cancer-directed, therapy. That said, the group as a whole demonstrated significantly compromised aerobic fitness (41% impaired), with enough fitness variability to investigate associations with outcomes of interest. Consistent with our second hypothesis, better motor proficiency and aerobic fitness were associated with better executive functions. This is a novel finding for pediatric brain tumor patients, particularly this early in treatment, but in keeping with correlational studies that indicate children of higher aerobic fitness outperform lower fit children on executive function and academic tasks (Chaddock, Hillman, et al., 2012; Fedewa & Ahn, 2011; Pontifex et al., 2011). These findings may help to explain differential risk/resiliency with respect to acute cognitive changes that may portend late effects among childhood brain tumor survivors. A more active premorbid lifestyle may enhance aerobic fitness that confers cognitive resilience. Alternatively, aerobic and cognitive fitness may share a genetic or biological resiliency with respect to acquired brain injury in keeping with cognitive reserve theories (Bigler & Stern, 2015; Mathias & Wheaton, 2015). It is possible that socioeconomic status could account for some of the shared variance, as children who come from families with greater opportunities for fitness-related activities may also have parents of higher cognitive functioning/education that in turn pass on and foster better executive functions (Ombrellaro et al., 2018). The pediatric oncology literature has also shown males are at less risk for cognitive late effects (e.g., Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001), with the current study showing males had less risk for endocrinopathies and better aerobic fitness early in treatment that perhaps serves as a buffer against emergence of cognitive late effects. Further, more aggressive surgical approach was associated with greater endocrinopathies and less aerobic fitness. There is some evidence in the literature that aggressive surgical approach to craniopharyngioma has greater cognitive consequence (Fournier-Goodnight, et al., 2017; Merchant et al., 2006) such that endocrinopathies and/or reduced aerobic fitness might serve as a moderator of cognitive risk.

Performance during fMRI exams revealed aerobic fitness was related to response accuracy and neural activation, as well as motor fitness. During a sensorimotor survey, activation patterns were consistent with primary sensory (visual and auditory) and motor cortex. Interestingly, increased activation in the left precuneus (part of the dorsal attention network) was associated with higher PKVO₂, suggesting those of higher fitness might be more engaged in a task of lower cognitive demand. Further, higher activity in insula, superior temporal and supramarginal areas was associated with increased BMI. Activation in the insula area has been associated with plasma levels of ghrelin, the gut hormone promoting appetite, possibly suggesting those with greater activity might have higher appetitive drives that could contribute to weight gain or increased BMI (Zanchi et al., 2017).

During the n-back task, activation patterns were consistent with a well established working memory network including robust activation in bilateral superior parietal lobule, dorsolateral prefrontal cortex, and middle and superior frontal gyri (Nee & Brown, 2013; Owen et al., 2005). Greater activation of posterior regions within this working memory network were associated with fewer commission errors, or more accurate performance. This finding is consistent with findings of Wolfe and colleagues (2013) who conducted a small (n= 9) fMRI study of working memory and its relationship with aerobic fitness in adolescent survivors of pediatric brain tumors (average of 10 years from treatment completion). They found individuals with higher aerobic fitness had better working memory performance on n-back tasks, as well as relatively greater activation of the well established working memory network during the 2-back condition. They interpreted their findings as indicative of more efficient functioning in frontal and parietal brain regions of interest for those of higher cardiorespiratory fitness (Wolfe et al., 2013). In the current study, greater activation (2-back > 0-back) of anterior and medial parietal regions within this working memory network were associated with better motor proficiency (BOT2). Activation of this subnetwork (green in Figure 2) connects motor proficiency to a focal subset (precuneus) of the extensive parietal areas associated with better n-back task performance (purple in Figure 2). The BOT2-associated precuneus node is adjacent to the PKVO₂-associated precuneus node detected in the sensorimotor survey (green in Figure 1), and both are within the dorsal attention network (Yeo et al., 2011). The imaging findings identify important associations among patterns of brain activation, fitness and executive functions and may provide clues to the neural mechanisms by which fitness and exercise affect cognitive function.

There is increasing appreciation for the role of aerobic exercise in preserving cognitive functioning and/or enhancing cognitive recovery, with candidate mechanisms identified through animal studies. Murine models have shown aerobic exercise improves brain structure through neurogenesis, synaptogenesis and angiogenesis, as well as increased production of neurochemicals (e.g., brain-derived neurotrophic factor) that promote growth, survival and repair of neurons (for review, see Voss et al., 2011). Multiple animal studies have shown voluntary exercise is associated with neurogenesis in the hippocampus, specifically, that correlates with improved performance on spatial memory tasks (Devine & Zafonte, 2009). Decreased hippocampal volumes, as well as reductions in normal appearing white matter, have been reported among childhood brain tumor survivors who underwent radiation therapy (e.g., Riggs et al., 2014; Reddick et al., 2005). Of note, the hippocampus and cerebral white matter are also two primary brain regions in humans where neural stem

cells are located (Ming & Song, 2011). These findings suggest aerobic training interventions may be beneficial for improving both medical (e.g., cardiopulmonary) and cognitive outcomes among pediatric oncology patients.

Devine and Zafonte (2009) conducted a review in which they found three out of four studies assessing cognitive benefits of exercise in individuals with acquired brain injuries showed better cognitive performance of those who exercised relative to those with brain injuries who did not exercise. The small number of exercise intervention studies conducted with children with cancer provide early evidence for feasibility and safety, as well as improvements in cardiopulmonary fitness, strength and fatigue (Huang & Ness, 2011). We are aware of only one exercise trial that measured cognitive outcomes in this population. Mabbott and colleagues conducted a controlled, cross over exercise trial (12-week structured aerobic exercise program with target heart rate monitoring) with 28 children who were long term survivors of brain tumors treated with cranial irradiation (Riggs et al., 2017). They found exercise-related reductions in reaction time across varied cognitive tasks that were predicted by white matter (fractional anisotropy), as well as exercise-related increases in hippocampal volume. This novel study demonstrated that exercise training can have beneficial impact on brain structure of childhood brain tumor survivors thus extending the findings of exercise-related neuroplasticity from animal models to humans. In the study conducted by Mabbott and colleagues (2017), brain tumor survivors were on average five years post diagnosis; current study findings indicate reduced aerobic fitness early in treatment, potentially suggesting a role for earlier exercise intervention.

This study is not without limitations. Presented analyses were cross-sectional and occurred prior to adjuvant cancer-directed therapy. While it is informative to see how early in treatment these children are experiencing cognitive, motor and aerobic fitness impairments, it will be important to follow them longitudinally to see how they do following radiation therapy. The cross-sectional design also means we cannot assume higher aerobic fitness caused better executive function; the design raises the possibility of a third variable (e.g., socioeconomic status) contributing to the relationship between aerobic fitness and cognitive performance. It will be important for future studies to measure and investigate the contribution of parental education and environmental resources to these relationships. The inclusion of functional neuroimaging in the current study is novel and assists with understanding the contributions of underlying neural activity to associations between fitness and cognitive performance. That said, inclusion of structural imaging would have further strengthened study design. Prior studies have found higher fit children have larger basal ganglia (Chaddock, Erickson, Prakash, VanPatter et al., 2010) and hippocampal volumes (Chaddock, Erickson, Prakash, Kim, et al., 2010), which is of interest given findings of decreased hippocampal volumes in children treated with radiation therapy for brain tumors. As it stands, it is unclear how brain volume differences/white matter connectivity contributed to current findings. Future studies should model the contribution of structural and functional plasticity in relation to aerobic fitness and cognitive performance. Finally, the current study investigated aerobic fitness as a cognitive/neuroimaging correlate but was not an exercise intervention study. Exercise intervention studies with the pediatric oncology population are just emerging with significant questions remaining regarding the best type, duration and timing of intervention. Future work should compare aerobic training with other

more direct cognitive interventions established in the literature such as psychostimulant medications (Conklin et al., 2010) or computerized cognitive training (Conklin et al., 2015). The incorporation of neuroimaging into these exercise studies will be instrumental to furthering understanding of exercise-related cognitive resiliency and neuroplasticity.

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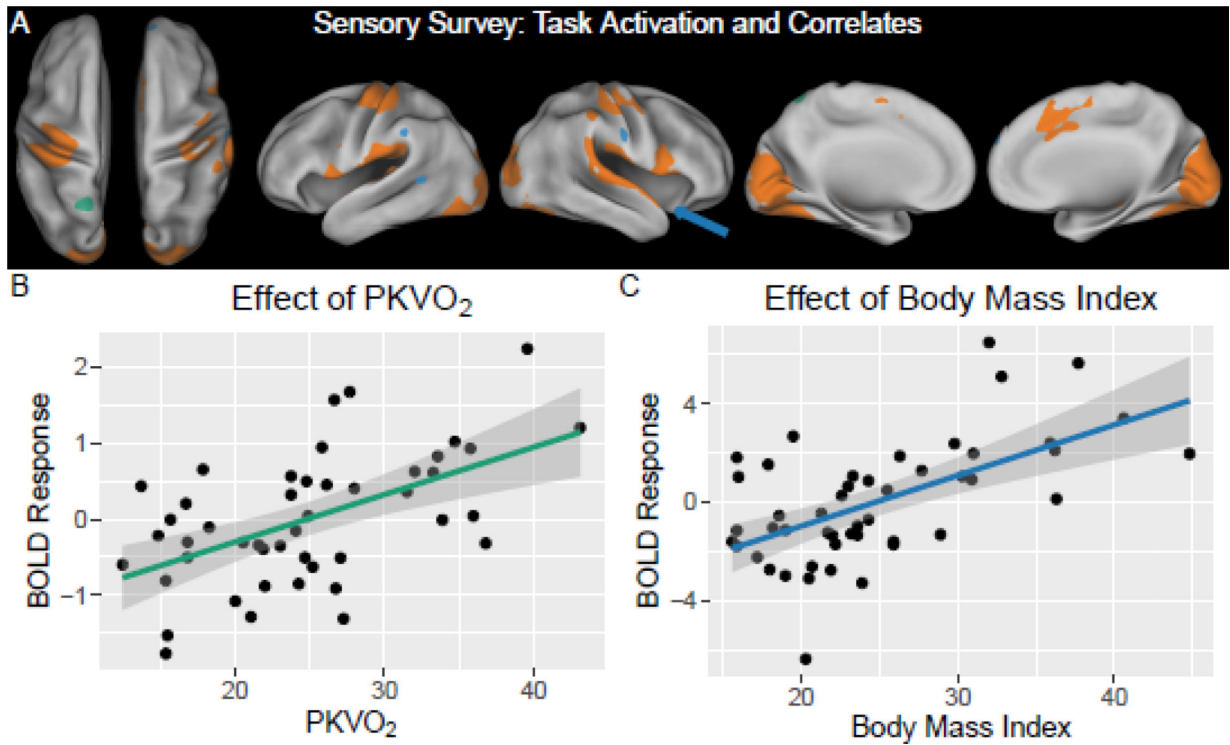


Figure 1. FMRI Findings during Sensorimotor Survey Task

(A) Orange overlay shows brain activation during visual, auditory and motor stimulation (contrast: task > rest in a random-effects group analysis; $p < 0.05$ with family-wise error [FWE] correction, minimum cluster size 200 voxels). Green overlay denotes an area where activity was positively associated with aerobic capacity (regression: task > rest versus PKVO₂; $p < 0.05$ with FWE correction, minimum cluster size 50 voxels). Blue overlay shows areas where brain activity was positively associated with body mass index (regression: task > rest versus body mass index measurements; $p < 0.05$ with FWE correction, minimum cluster size 50). (B) Scatter plot of activity versus PKVO₂ at the cluster located in the left precuneus. (C) Scatter plot of activity versus BMI at the cluster in the right insula/temporal pole, identified by the arrow in (A).

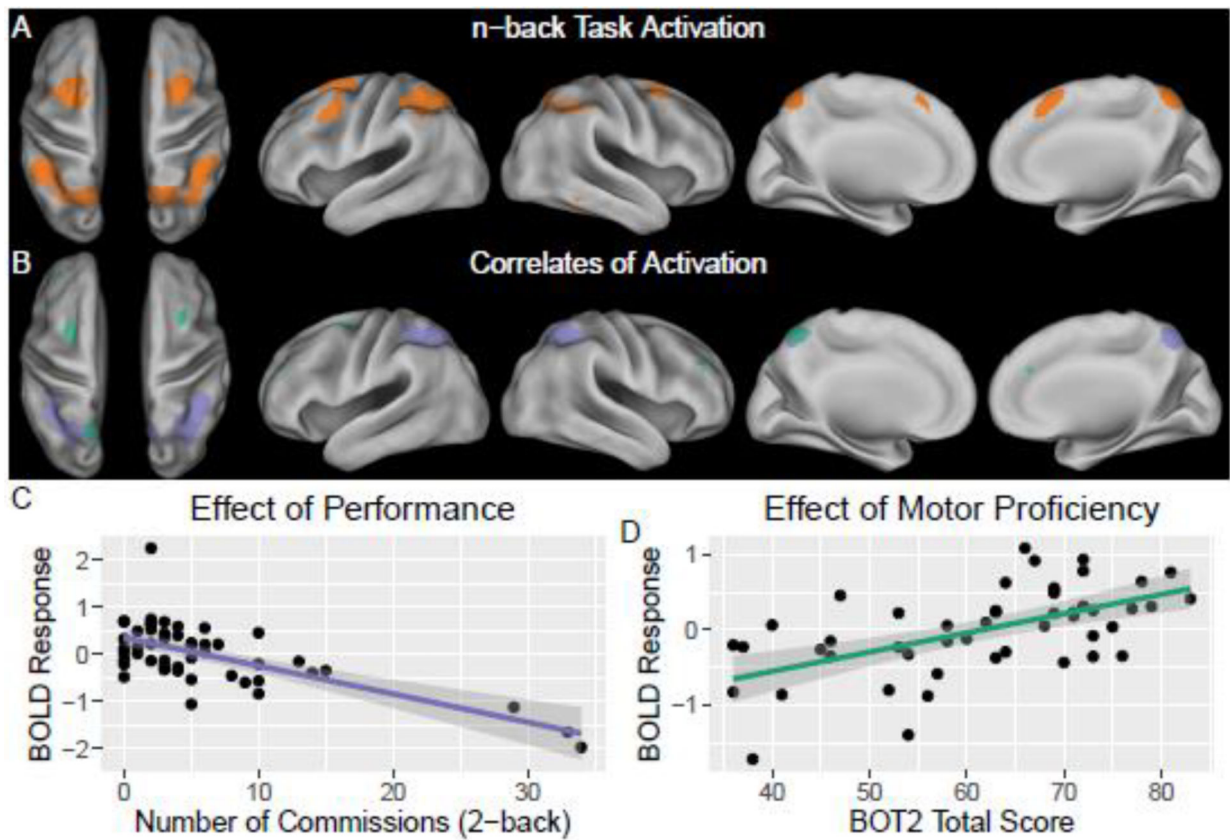


Figure 2. FMRI Findings during N-back Working Memory Task

(A) Orange overlay shows brain activation during n-back task (contrast: 2-back > 0-back in a random-effects group analysis; $p < 0.05$ with family-wise error [FWE] correction, minimum cluster size 200 voxels). (B) Neural correlates of performance and motor proficiency. Light purple denotes areas where activity was negatively associated with commission errors during the task (regression: 2-back > 0-back versus commission errors during the 2-back task; $p < 0.05$ with FWE correction, minimum cluster size 200 voxels). Green overlay shows areas where brain activity was positively associated to motor proficiency (univariate regression: 2-back > 0-back versus BOT2 total scores; $p < 0.05$ with FWE correction, minimum cluster size 200; clusters drop just below FWE significance ($P \sim 0.1$) with age in the model but demonstrate consistency across all models examined). (C) Scatter plot of activity versus commission errors at a sub-cluster in the right superior parietal lobule. (D) Scatter plot of activity versus BOT2 scores at cluster in the left superior frontal gyrus.

Table 1

Demographic and Clinical Characteristics

		<i>n</i>	(%)
Gender			
Male		50	48.1
Female		54	51.9
Race			
Caucasian		68	65.4
African American		16	15.4
Asian		4	3.8
Other ^a		16	15.4
Extent of Surgical Resection			
No surgery		12	11.5
Catheter only		17	16.4
Resection		75	72.1
Cerebral Spinal Fluid Diversion ^b			
No		70	67.3
Yes		34	32.7
Diabetes Insipidus ^c			
No		49	47.1
Yes		55	52.9
	<i>n</i>	<i>M (SD)</i>	Range
Age at Baseline (Years)	104	10.0 (4.6)	1.0 – 20.2 ^d
Number of Surgeries	104	1.5 (1.2)	0 – 8
Time Since Surgery (Months) ^e	92	6.5 (10.3)	0.2 – 50.3
Body Mass Index	95	22.6 (6.2)	14.3 – 44.8
PKVO ₂	88	23.9 (7.1)	8.3 – 43.1
BOT2 ^f	86	38.6 (9.0)	20 – 61
Wechsler IQ ^g	93	100.8 (16.0)	56 – 130

^aOther race was composed of participants with race marked as “unknown”.

^bIncludes patients who received either ventriculoperitoneal shunting or endoscopic third ventriculostomy.

^cDetermined based on whether patient was prescribed desmopressin prior to baseline cognitive evaluation.

^dCognitive data was not gathered for children under 2 years (*n* = 2).

^eDoes not include patients who did not have surgery.

^fBruinicks-Oseretsky Test of Motor Proficiency, Second Edition; age standardized with a mean of 50 ± 10.

^g8 subtest pro-rated IQ score from the age-appropriate Wechsler measures; age standardized with mean of 100 ± 15.

Table 2

Correlations among Demographic/Clinical Factors with Cognitive and Fitness Measures

Measures	N ^a	Age	Gender	BMI	Number of Surgeries	Extent of Resection	DI
Wechsler IQ	93	-.01	-.14	.03	-.06	-.14	.11
CPT-II Omissions	67	-.09	.22	-.09	.15	.26*	.10
CPT-II Commissions	67	-.05	.07	-.02	.15	.26*	.24
CPT-II Hit RT	67	.06	.17	-.07	-.04	-.03	-.03
Wechsler WMI	81	-.06	-.13	-.04	-.09	-.08	.06
WJ-III Retrieval Fluency	87	-.10	.06	-.05	-.15	-.16	-.01
D-KEFS CWI	52	-.20	-.17	-.03	.02	-.01	-.05
BRIEF WM	98	-.15	-.01	-.01	.08	.02	0.17
BRIEF MCI	78	-.07	-.03	-.02	.06	.11	.18
BRIEF BRI	79	-.06	-.10	.14	.22	-.06	.18
BRIEF GEC	97	-.17	-.09	.00	.14	.02	.18
WJ-III LWI	76	.01	-.12	.05	.07	.00	.12
WJ-III Calculation	74	.08	-.12	.20	.06	.03	.16
BOT2	86	-.03	-.06	-.14	-.42***	-.18	-.23*
PKVO ₂	88	.29**	-.33**	-.24*	-.34**	-.26*	-.28**
DI	104	-.10	.21*	.10	.28**	.42***	-----

^aSample size for correlations is decided by sample size for cognitive measures except for BMI ($n=95$); Age, Gender, Number of Surgeries, Extent of Resection and DI have a sample size of 104. Note.> Pearson correlations computed to assess association for two continuous variables, Spearman for an ordinal and continuous variable or binary variable, and Point-biserial for a binary and continuous variable. Coding for correlations: Gender-Male= 1, Female= 2; Extent of Resection- No Surgery= 1, Catheter Only= 2, Resection= 3; DI- No=0, Yes=1 *BMI* Body Mass Index, *DI* Diabetes Insipidus, *IQ* Intelligence Quotient, *CPT-II* Conners' Continuous Performance Test, Second Edition, *RT* Reaction Time, *WMI* Working Memory Index, *WJ-III* Woodcock Johnson, Third Edition, *D-KEFS* Delis-Kaplan Executive Function System, *CWI* Color-Word Interference, *BRIEF* Behavior Rating Inventory of Executive Function, *WM* Working Memory, *MCI* Metacognitive Index, *BRI* Behavior Regulation Index, *GEC* Global Executive Composite, *LWI* Letter-Word Identification, *BOT2* Bruinicks-Oseretsky Test of Motor Proficiency, Second Edition

 $p < .001$,

**
 $p < .01$,

*
 $p < .05$

Table 3

Correlations among Fitness Indicators and Cognitive Measures

	PKVO ₂		BOT2	
	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>
Wechsler IQ	82	.20	78	.23 ^{*a}
CPT-II Omissions	65	-.20	63	-.26 [*]
CPT-II Commissions	65	-.06	63	-.17
CPT-II Hit RT	65	.00	63	-.25 [*]
Wechsler WMI	76	.27 ^{*a}	74	.32 ^{***a}
WJ-III Retrieval Fluency	83	.23 ^{*a}	80	.32 ^{***a}
D-KEFS CWI	51	.14	50	.27
BRIEF WM	85	-.05	82	-.20
BRIEF MCI	74	.00	72	-.28 ^{*a}
BRIEF BRI	75	-.06	72	-.35 ^{***a}
BRIEF GEC	84	-.07	82	-.19
WJ-III LWI	73	.13	70	.12
WJ-III Calculation	71	.24 [*]	68	.19

Note. Pearson correlations computed to assess association for two continuous variables *IQ* Intelligence Quotient, *CPT-II* Conners' Continuous Performance Test, Second Edition, *RT* Reaction Time, *WMI* Working Memory Index, *WJ-III* Woodcock Johnson, Third Edition, *D-KEFS* Delis-Kaplan Executive Function System, *CWI* Color-Word Interference, *BRIEF* Behavior Rating Inventory of Executive Function, *WM* Working Memory, *MCI* Metacognitive Index, *BRI* Behavior Regulation Index, *GEC* Global Executive Composite, *LWI* Letter-Word Identification, *BOT2* Bruinicks-Oseretsky Test of Motor Proficiency, Second Edition.

**
p < .01,

*
p < .05,

^a Statistical results remained significant after accounting for multiple comparisons using the False Discovery Rate within measures.

Table 4

fMRI Activation Coordinates

Area	Peak T-value	X	Y	Z	Cluster Size (voxels)
Sensorimotor Survey					
<i>Task</i>					
Lingual Gyrus	16.16	-14	-90	-14	12,232
Lingual Gyrus	15.66	12	-94	-6	
Calcarine Sulcus	15.24	2	-88	-6	
Precentral Gyrus	12.12	-34	-26	56	4442
Precentral Gyrus	11.35	-38	-22	62	
Postcentral Gyrus	10.67	-46	-22	60	
Precentral Gyrus	11.26	36	-24	60	1173
Inferior Parietal Lobule	8.26	54	-34	54	
Precentral Gyrus	8.21	50	0	52	
Temporal Pole	10.81	54	14	-4	3471
Temporal Pole	10.48	56	6	0	
Superior Temporal Gyrus	9.55	64	-14	8	
Mid-Cingulate Area	8.42	4	16	44	980
Supplemental Motor Area	8.41	0	-4	56	
Supplemental Motor Area	7.78	2	4	48	
<i>PKVO2</i>					
Precuneus	4.28	-2	-54	68	74
<i>Body Mass Index</i>					
Insula	4.94	48	16	-12	320
Post Central Gyrus	4.31	60	-14	36	161
Supramarginal Gyrus	4.38	-58	-42	36	113
Middle Temporal Gyrus	4.34	-56	-52	6	403
N-Back					
<i>Task</i>					
Superior Frontal Gyrus	7.8	26	4	64	969
Precuneus	7.33	-12	-70	58	5398
Precuneus	6.76	12	-68	56	
Inferior Parietal Lobule	6.56	-42	-46	48	
Middle Frontal Gyrus	7.26	-26	6	62	1453
Precentral Gyrus	4.12	-36	-2	42	
Precentral Gyrus	3.90	-44	2	46	
Supplementary Motor Area	6.21	0	18	52	703
Middle Frontal Gyrus	4.68	-36	56	18	165
Middle Frontal Gyrus	4.22	-36	56	8	
Middle Frontal Gyrus, Orbital	3.66	-44	48	0	

Area	Peak T-value	X	Y	Z	Cluster Size (voxels)
Sensorimotor Survey					
<i>Commission Errors</i>					
Middle Occipital Gyrus	5.54	30	-62	38	1556
Inferior Parietal Lobule	5.29	32	-44	42	
Angular Gyrus	4.56	26	-58	42	
Inferior Parietal Lobule	5.50	-30	-44	52	2644
Superior Parietal Lobule	5.45	-28	-58	52	
Inferior Parietal Lobule	5.20	-26	-58	42	
<i>BOT2 score*</i>					
Precuneus	5.08	-14	-64	50	2051
Superior Parietal Lobule	4.22	-14	-64	56	
Superior Parietal Lobule	4.08	-18	-58	52	
Precentral Gyrus	4.74	-34	-2	38	863
Frontal Middle Gyrus	4.49	-26	-2	52	
Superior Frontal Gyrus	3.79	-20	8	64	
Middle Frontal Gyrus	4.60	28	12	58	2787
Insula	4.32	36	28	32	
Inferior Frontal Gyrus, Opercularis	4.21	40	18	8	

Note. All results shown are $p < 0.05$ FWE corrected for multiple comparisons. All results are controlled for age except for BOT2 scores, which fall below FWE threshold with age in the model, but clusters were consistent across all models evaluated.