Repairing the Brain with Physical Exercise: Insights from Cortical Thickness Analysis of An Exercise Trial in Pediatric Brain Tumor Survivors

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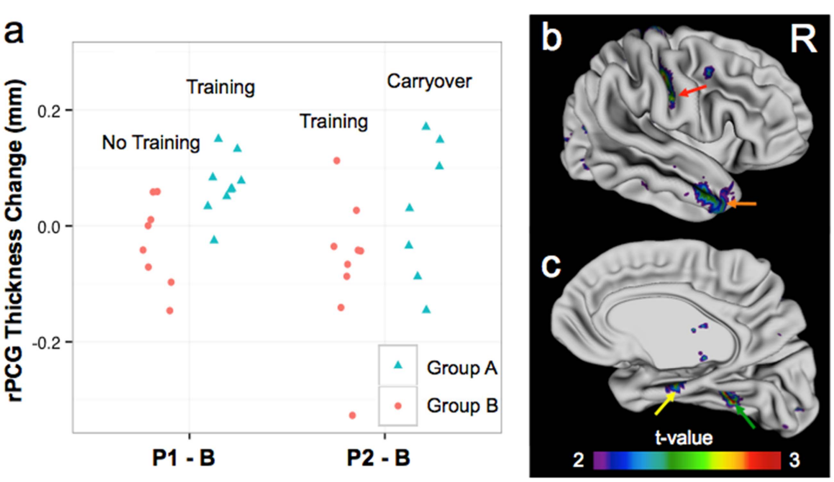
Target Audience: Clinicians, brain tumor survivors and their families and caregivers, as well as neuroscientists interested in brain plasticity and/or brain repair processes will benefit from learning about this work.

Purpose: Cranial radiation is a standard form of treatment for malignant brain tumors. While radiation increases survival rates, it also leads to long-term cognitive impairments and neurodegeneration [1-4]. Unfortunately, there is no cure or standard of care for these treatment-related effects. Recently, there have been a growing number of studies showing the benefits of physical activity for the brains of healthy children [5-6], but its potential as a rehabilitative technique remains unknown. We conducted a 12-week program to examine whether aerobic exercise can stimulate brain repair processes in pediatric brain tumor survivors treated with cranial radiation. Specifically, we examined the effects of exercise on cortical thickness.

Methods: We employed a waitlist control cross-over design. 18 children treated for brain tumors participated in 90-minutes of group based aerobic activities 3 times per week for 12 weeks. 9 children out of this group (age = 10.9 ±2.6) were assigned to start training first (Group A), and 9 children (Age = 12.2 ±3.4) were assigned to wait 12 weeks and then start training (Group B). Participants in the Group A were scanned at the beginning of the exercise program (Baseline), post-intervention (Period 1) and 3 months after cessation of the exercise program (Period 2). Group B participants were scanned 3 month before starting the exercise program (Baseline), at the beginning of the exercise program (Period 1) and post-intervention (Period 2). MR data were collected at The Hospital for Sick Children using either a GE Signa HDxt 1.5T MRI scanner (n=5) with an 8-channel head coil (GE Healthcare, Milwaukee, Wisconsin) or Siemens Tim Trio 3T MRI scanner (n=13) with a 12-channel head coil (Siemens Canada Ltd., Mississauga, Ontario). Imaging parameters for 3D-T1 FSPGR, anatomical images, acquired at 1.5T were: inversion time = 400 ms; TE/TR = 4.2/10.1 ms; flip angle = 90º, 116–124 contiguous axial slices; 256 × 192 matrix, interpolated to 256 × 256; FOV = 25.6 × 22.4 cm; voxel size = 0.9375x0.9375 mm, slice thickness = 1.5 mm. At 3T 3D-T1 MPRAGE with the following parameters was used: Grappa = 2, TE/TR = 3.9/2300 ms, flip angle = 9º, 160 contiguous axial slices, 256 × 224 matrix, FOV = 25.6 × 22.4 cm, voxel size = 1 mm iso. Data were processed with CIVET as described in [7] and [8]. For each subject, cortical thickness at a Baseline was subtracted out from thickness estimates at Period 1 and 2 and subsequent analyses were done on the difference from the Baseline. A region of interest (ROI) approach as well as vertex-wise statistics across entire cortical surface were used to analyze changes in cortical thickness in response to the exercise intervention. Statistical significance of these changes was assessed using linear mixed effects model.



Results and Discussion: Regional analysis of changes in cortical thickness (one potential outlier removed) revealed a significant effect of time (-0.14 mm, $p<0.01$), training (0.1 mm, $p<0.05$) and carryover (0.19 mm, $p<0.01$) on thickness of right precentral gyrus (rPCG; Fig. a and b-red arrow). The significant carryover effect in the treatment group is especially interesting as it indicates that even after cessation of the program, prior exercise continues to exert an effect on the brain. Additionally, based on whole brain vertex-wise analysis, interesting trends of increase in cortical thickness were seen within: the right and left temporal pole (Fig. 1b-orange arrow), the right postcentral gyrus, right parietal lobe, right and left entorhinal cortex (Fig. 1c-green arrow), and the right and left parahippocampal gyrus (Fig. 1c-yellow arrow).

Conclusions: We have previously shown statistically significant increases in hippocampal volume (4.4%) in response to training using a manual ROI analysis of this data set. Although, changes in the hippocampus were much more pronounced than in the cortex, together this data suggest that aerobic exercise may be an effective intervention in fostering neuro-recovery in children treated for brain tumors with radiation. Future work will examine the relation between changes in brain structure and cognitive functioning.

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